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(73) Proprietor: **AMERSHAM INTERNATIONAL plc**
Amersham Place
Little Chalfont
Buckinghamshire HP7 9NA (GB)

(72) Inventor: **ARCHER, Colin Mill**
Amersham International plc,
Amersham Place
Little Chalfont,
Buckinghamshire HP7 9NA (GB)
Inventor: **DILWORTH, Jonathan Robin, Dept.**
of Chemistry and
Biol. Chemistry,
University of Essex, Wivenhoe Park
Colchester,
Essex C04 3SQ (GB)
Inventor: **JOBANPUTRA, Panna**
27 Sinnington End,
Highwoods
Colchester,
Essex C04 4RE (GB)

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EP 0 441 953 B1

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Inventor: LATHAM, Ian Andrew

Amersham International plc,
Amersham Place

Little Chalfont,

Buckinghamshire HP7 9NA (GB)

Inventor: THOMPSON, Russell Martin, Dept. of

Chemistry and

Biol.Chemistry,

University of Essex, Wivenhoe Park

Colchester,

Essex C04 3SQ (GB)

⑦ Representative: Gaunt, Robert John et al
Stevens, Hewlett & Perkins
1 Serjeants' Inn
Fleet Street
London EC4Y 1LL (GB)

Description

This invention relates to novel complexes of technetium (Tc), containing the moiety $Tc=NR$, $Tc-N=NY$ or $Tc(-N=NY)_2$, and their use in radiopharmaceuticals for a variety of clinical applications. Methods for the preparation of the technetium complexes are also described.

Radiopharmaceuticals may be used as diagnostic or therapeutic agents by virtue of the physical properties of their constituent radionuclides. Thus, their utility is not based on any pharmacologic action. Most clinically used drugs of this class are diagnostic agents incorporating a gamma-emitting nuclide which, because of physical or metabolic properties of its co-ordinated ligands, localises in a specific organ after intravenous injection. The resultant images can reflect organ structure or function. These images are obtained by means of a gamma camera that detects the distribution of ionising radiation emitted by the radioactive molecules. The principal isotope currently used in clinical diagnostic nuclear medicine is metastable technetium-99m (^{99m}Tc) and which has a half-life of 6 hours.

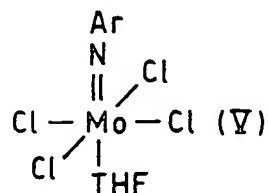
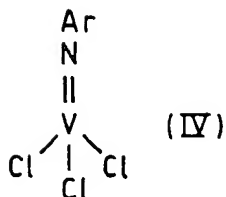
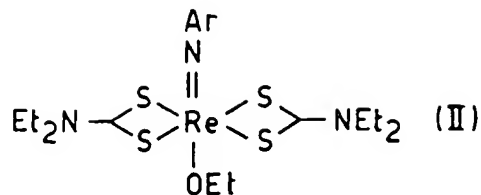
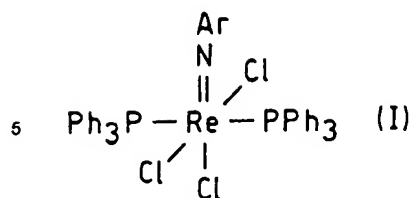
The preparation of ^{99m}Tc radiopharmaceuticals generally requires addition of generator-produced $Na^{99m}TcO_4$ eluate to a ligand or ligands in the presence of a reducing agent. Many reducing agents have been used to this effect including tin metal, stannous ion, sodium borohydride, ferrous ascorbate, ferrous ion and formamidine sulphonic acid. These procedures often lead to Tc complexes containing the $Tc=O$ moiety, where the technetium is in the +4 or +5 oxidation state. The formation of such radiopharmaceutical complexes can often occur via substitution reactions on $[Tc^VOX_5]^{2-}$ or $[Tc^VX_6]^{2-}$ molecules, which has been identified as a route of significant synthetic utility (Deutsch E, Libson K, Jurisson S, Lindoy L F, Technetium Chemistry and Technetium Radiopharmaceuticals, Prog. Inorg. Chem. (1982) 30 p 175). Only under harsh reaction conditions in the presence of powerful reducing agents and/or strong acids or bases are Tc^I oxidation state complexes attained and stabilised. A limitation to the formation of novel radiopharmaceutical products is the tendency towards formation of $Tc=O$ species, but in addition formation of Tc^{4+} or Tc^{5+} complexes also limits the number and/or type of ligands prone to bind to the metal.

PCT Application WO 85/03063 describes the synthesis of the $Tc=N$ moiety as an intermediate in the preparation of radiopharmaceuticals by virtue of its ability to undergo various ligand substitution reactions. The $Tc=N$ core is again primarily based on the +5 oxidation state of Tc.

The reaction of $TcCl_6^{2-}$ with hydroxylamine salts under a variety of conditions to form a variety of complexes containing the $Tc-NO$ moiety has been described (Eakins, JCS (1963) 6012; Radnovich and Hoard, J. Phys. Chem. 88 (26) (1984) 6713; Armstrong and Taube, Inorg. Chem. (1976) 15 (3), 1904). This literature is concerned with ^{99}Tc and not with its metastable isotope ^{99m}Tc . ^{99}Tc has a half-life of 2.1×10^5 years, decays by emitting beta particles, and is of no interest as a radiopharmaceutical.

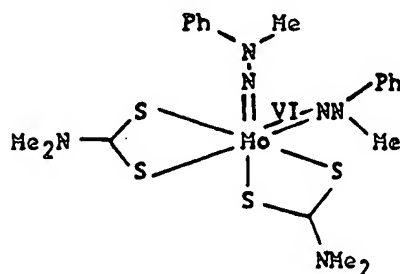
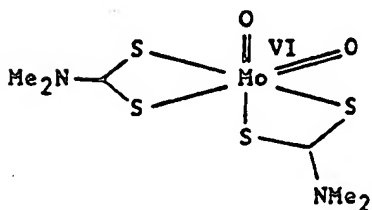
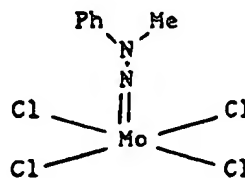
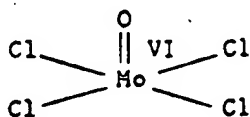
European Patent Application No. 0 291 281 A describes technetium complexes containing the $^{99m}Tc-NO$ moiety, together with a ligand which confers biological target-seeking properties on the complex, and their use as radiopharmaceuticals. The complexes are made from pertechnetate (TcO_4^-) by a variety of routes involving hydroxylamine salts. Studies of the coordination chemistry of technetium have generally been directed towards the synthesis and development of new ^{99m}Tc labelled radiopharmaceuticals. ¹ The majority of the technetium containing radiopharmaceuticals currently in clinical use involve technetium complexes containing either a mono-oxo or di-oxo core, i.e. $[Tc^V=O]^{3+}$ or $[Tc^VO_2]^+$ respectively. ^{1,2} Technetium (V) oxo-species are used to image kidney, liver, brain and bone tissues.

The terminal imido (2-) moiety, $=NR$, is formally isoelectronic to a terminal oxo (2-) function, $=O$. Many transition metal complexes containing an organo-imido ligand are known³. Examples include the following complexes based on rhenium ^{4,5,6}, (I, II), tungsten⁷ (III), vanadium⁸ (IV) and molybdenum⁹ (V):-



where Ar is an aryl group.

When the R substituent of a terminal imide ligand is a dialkyl amide moiety, NY_2 , the imide ligand is more often described as a hydrazide (2-) ligand. Thus the terminal hydrazido (2-) moiety, $=\text{N}-\text{NR}_2$, is also isoelectronic to a terminal oxo (2-) function, and many transition metal complexes containing hydrazido (2-) ligands are known¹⁰. Examples of isostructural metal-oxo and metal-hydrazido (2-) complexes include the following^{11,12,13,14}:-



Similarly, the diazenido moiety, $=\text{N}=\text{NR}$, is isoelectronic and isostructural with the nitrosyl ligand ($=\text{NO}$).

Unlike oxo- and nitrosyl ligands, however, imide (2-), hydrazido (2-) and diazenido ligands can carry a variety of different substituents on the nitrogen atom which is not bound to the metal atom. The presence of any of these three moieties in a technetium complex therefore permits the preparation of new radiopharmaceuticals with a variety of biological characteristics which can be modulated by varying or altering the R substituents. In addition, the methods for the synthesis of complexes containing $\text{Tc}=\text{NR}$, $\text{Tc}=\text{N}-\text{NY}_2$ or $\text{Tc}=\text{N}=\text{NY}$ moieties are compatible with the concomitant ligation of a wide variety of other ligands. It is this discovery which forms the basis of the present invention.

According to this invention there is provided a complex of technetium (^{99}Tc or $^{99\text{m}}\text{Tc}$) which contains the moiety $\text{Tc}=\text{NR}$, $\text{Tc}=\text{N}=\text{NY}$ or $\text{Tc}(\text{N}=\text{NY})_2$, and a ligand which confers biological target-seeking properties on the complex, wherein

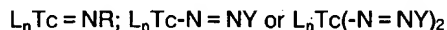
R represents an aryl group, a substituted or unsubstituted alkyl group, or the grouping $=\text{NR}^1\text{R}^2$;

Y represents an aryl group or a substituted or unsubstituted alkyl group;

and

R¹ and R² are hydrogen, aryl groups or substituted or unsubstituted aliphatic or cyclic alkyl groups, and may be both the same or different, provided that both are not hydrogen.
The complex is useful as a radiopharmaceutical.

5 Complexes in accordance with this invention have the formulae:



wherein

10 L represents a mono- or multi-dentate ligand;
n is 1, 2, 3 or 4

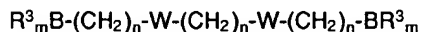
and

R and Y are as defined above.

The alkyl group substituents may be aliphatic (straight chain or branched) or cyclic, and may be substituted with, for example, oxygen, nitrogen, sulphur and/or phosphorus.

A wide range of ligands for these complexes are envisaged, including:-

a) Phosphines and arsines of the general formula Q₂B(CD₂)_nBQ₂, where B is P or As; Q is H or aryl or substituted or unsubstituted alkyl, preferably C1 - C4 alkyl or phenyl; n is 1, 2, 3 or 4; and (CD₂) is a substituted or unsubstituted methylene group. Related compounds are described in:-
20 US 4481184, US 4387087, US 4489054, US 4374821, US 4451450, US 4526776, EP-A-0266910 (Amersham International; methylene bridged diphosphine complexes), EP-A-0311352 (Amersham International; phosphines containing ether groups), and ligands of general type



25

where

B is P or As,

W is NR, S, Se, O, P or As,

R³ is H or hydrocarbon such as C1 - C6 alkyl or aryl,

30 m is 1 or 2, and

n is 1, 2, 3 or 4.

b) Methylene Diphosphonate (MDP)

c) Thiourea (TU)

d) Thiomalate (TMA)

35 e) Dimercaptosuccinic acid (DMSA)

f) Gluconate (GLUC)

g) Ethane-1-hydroxy-1,1-diphosphonate (EHDP)

h) Diethylene triamine pentaacetic acid (DTPA)

i) N-(2,6-[Dialkyl]phenyl carbamoylmethyl) iminodiacetate

40 alkyl = Methyl (HIDA)

Ethyl (EHIDA)

Propyl (PIPIDA)

j) Dialkyl dithiocarbamate

k) Isonitriles of the general type C≡NR⁴ R⁴ = alkyl, alkoxy, ether

45 l) BAT Derivatives - of the general type illustrated below, and specifically:

i) R⁵ = R¹¹ = H

R^{6,7,9,10} = Et

R⁸ = N-methylspiropiperidiny

ii) R⁵ = R¹¹ = H

50 R^{6,7,9,10} = Et

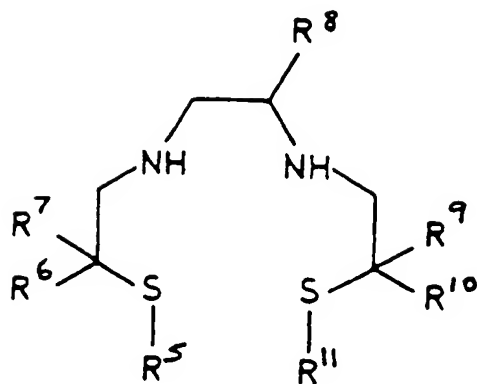
R⁸ = N-ethylspiropiperidiny

iii) R⁵ = R¹¹ = H

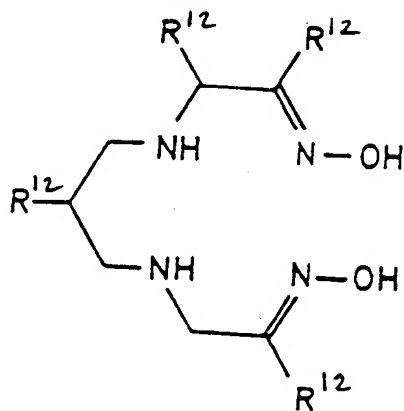
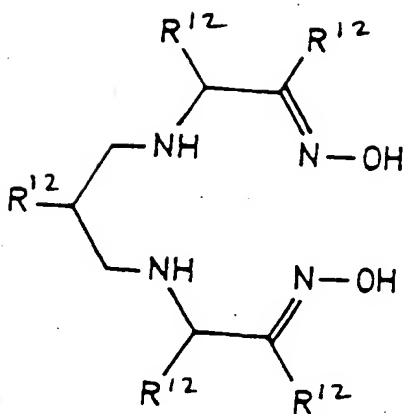
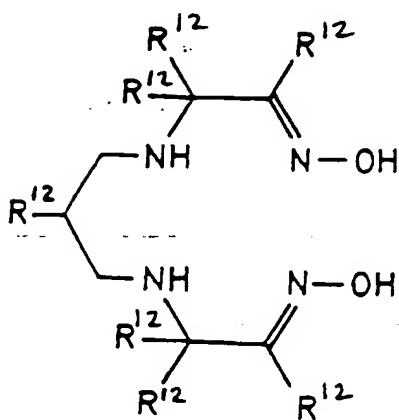
R^{6,7,9,10} = Et

R⁸ = N-isopropylspiropiperidiny

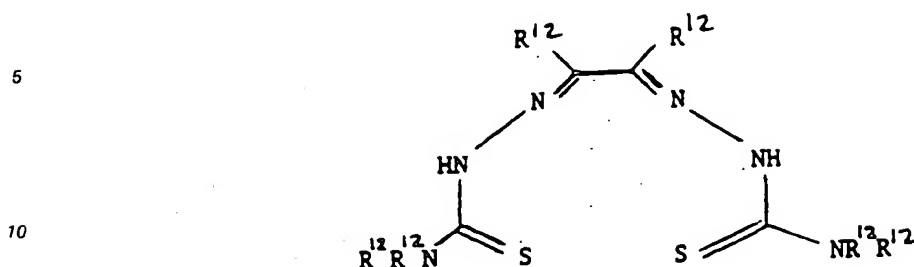
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- m) phenanthroline,
 n) pentane-2,4 -dione,
 o) bipyridyl,
 p) Other ligands having propylene amine oxime backbone of the general structural types described in
 EPA 123504 and 194843:



q) Bisthiosemicarbazones of the formula:



where the various groups R^{12} can be the same or different and are H and/or alkyl and/or aryl substituents.

15 Other suitable ligands are shown in Table 1.

The invention further provides methods for the preparation of the aforementioned complexes of technetium. One such method involves the derivatisation of technetium oxo-containing species by condensation with hydrazines or amines (equation A), isocyanates (equation B), sulphinylamines (equation C) or phosphinimines (equation D):-

20



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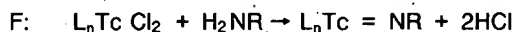
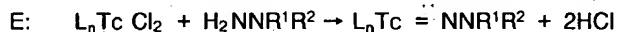
wherein R, L and n are defined as above.

30

The driving force for these reactions is the formation of a stable product containing the former oxo function (i.e. water, carbon dioxide, sulphur dioxide or phosphine oxide), which is generally easily removed after the oxo group transfer, leaving the desired technetium hydrazido (2-) or imido complex.

An alternative method of preparation involves the reaction of hydrazines (equation E) or amines (either aliphatic or aromatic) (equation F) with complexes containing technetium-halogen bonds:-

35



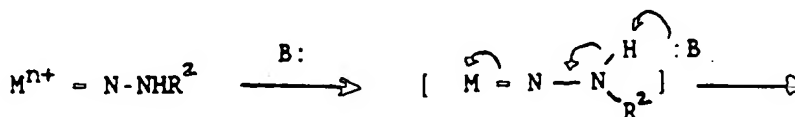
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where L, R, R^1 and R^2 are as previously defined.

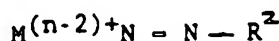
The driving force for these reactions is the concomitant formation of the volatile, easily removed hydrogen halide during the metathesis reaction.

It will be appreciated that the hydrazides and diazenides can be considered as essentially being functionalised imide ligands. The hydrazide (2-) ligand, $=NNR^1R^2$, is just the imide ligand, $=NR$, where R is NR^1R^2 ; and the diazenide ligand results when R^1 is hydrogen. In this case, the intermediate hydrazide (2-) complex is deprotonated by a base to give a metal-diazenide complex with concomitant reduction of the metal centre:

50



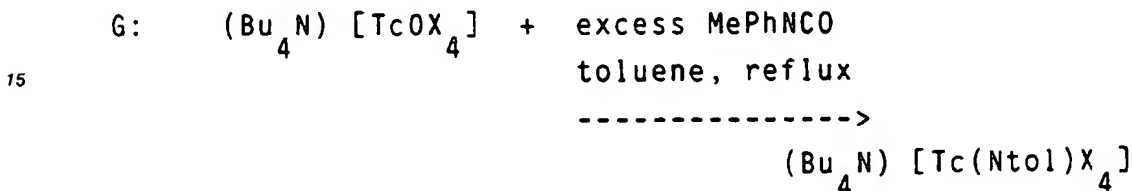
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In the reactions reported herein, the base is always the added excess of hydrazine in the solution.

Turning now to the preparation of the technetium complexes containing an imido moiety, the approach has been to replace the oxo function in $[\text{TcOX}_4]^-$ ($X = \text{Cl}, \text{Br}$) using arylisocyanates (reaction type equation B). This formed a convenient entry point into the work by extending an established route for the synthesis of $\text{Tc}=\text{NR}$ complexes. This method has only been previously used for generation of neutral imido products from neutral transition metal oxo starting materials.¹⁷ The work reported here is thus the first example of the method extended to the preparation of anionic transition metal imido complexes, and also to technetium chemistry.

Reaction of $[\text{Tc}^{\text{V}}\text{OX}_4]^-$ with excess ArNCO in refluxing dry toluene under nitrogen gives excellent yields of the desired Tc^{V} -imido products isolated as solids on ether trituration of the residue obtained directly from the reaction mixture (equation G):-



X = Cl, 95-100 % 1

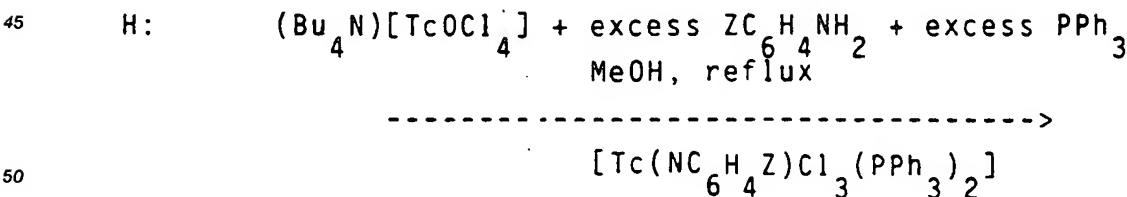
X = Br, 74 % 2

Even though the method gives good yields of reasonably pure solids, the reaction is not trivial. The starting isocyanates are quite moisture and air sensitive such that the reaction must be strictly performed under an atmosphere of N_2 . 1 and 2 are black-blue solids that are also quite sensitive to adventitious moisture, however, they are stable under dry N_2 . That the products are very sensitive to moisture is evidenced by the fact that if reagent grade diethyl ether is used in the trituration phase of the workup procedure instead of anhydrous ether, then the product is isolated as a red-brown insoluble polymeric compound. The products also do not always chromatograph (HPLC) satisfactorily.

The products $[\text{Tc}(\text{Ntol})\text{X}_4]^-$ contain the new core moiety $[\text{Tc}^{\text{V}}=\text{NR}]^{3+}$ which is formally analogous to the well known $[\text{Tc}=\text{O}]^{3+}$ core. $[\text{Tc}(\text{NR})\text{X}_4]^-$ is a sixteen electron species in which the imido ligand functions as a four electron donor; the technetium-nitrogen bond is therefore expected to be a short, linear multiple $[\text{Tc}=\text{NR}]$ bond. Attempted structural characterisation of $[\text{Tc}(\text{Ntol})\text{Cl}_4]^-$ as its PPh_4^+ salt by X-ray crystallography has so far been unsuccessful due to its sensitive nature. The products 1 and 2 are very good starting materials for the preparation of many new $\text{Tc}=\text{NR}$ complexes.

In view of the somewhat sensitive nature of 1 and 2, investigation of much more stable Tc -imido complexes was undertaken. The direct metathesis reactions of $[\text{TcOCl}_4]^-$ with aromatic amines was undertaken in the presence of phosphine ligands. Reactions of this type may show promise in $^{99\text{m}}\text{Tc}$ chemistry in view of the wide variety of substituted aromatic amines available commercially.

Reaction of $[\text{TcOCl}_4]^-$ with ArNH_2 in refluxing MeOH in the presence of the monodentate phosphine PPh_3 gives the green-brown neutral Tc^{V} imido complexes which analyse for $[\text{Tc}(\text{NR})\text{Cl}_3(\text{PPh}_3)_2]$ (equation H):-



3 Z = CH_3

4 Z = Br^3

5 Z = Cl

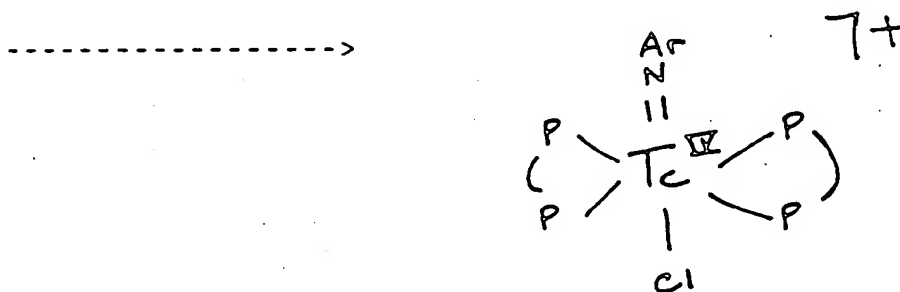
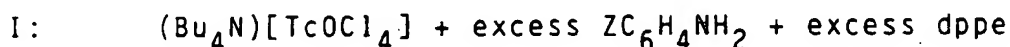
Chromatographic analysis (HPLC, beta detection) of these products show only one significant ^{99}Tc -containing species. These neutral Tc^{V} complexes also contain the new $[\text{Tc}^{\text{V}}=\text{NR}]^{3+}$ core. They are diamagnetic, air-stable solids which are very soluble in CH_2Cl_2 , CHCl_3 , moderately soluble in alcohols, and

insoluble in ether and petrol. They exhibit a singlet (ca. 30 ppm) in the ^{31}P NMR spectrum, indicating two trans- PPh_3 groups in identical environments. Structural characterisation of 3 by X-ray has now been carried out and Figure 1 gives a Ball and Stick representation of the complex molecule. The diagram shows a linear tolylimide group and the two PPh_3 groups to be trans. The $[\text{Tc}=\text{Ntol}]$ unit in 3 may therefore be correctly assigned as a linear four electron donor imido ligand, and the complex is formally an 18-electron species.

This work therefore represents the first structurally characterised Tc^{V} -imido complex.

The $[\text{Tc}(\text{NR})\text{Cl}_3(\text{PPh}_3)_2]$ compounds are much superior starting materials than $[\text{Tc}(\text{NR})\text{X}_4]^-$ because these are much more stable $\text{Tc}=\text{NR}$ species.

Reaction of $[\text{TcOCl}_4]^-$ with excess amine and dppe in refluxing MeOH or EtOH allows the isolation of good yields of the cationic Tc-imido complexes $[\text{Tc}^{\text{V}}(\text{NC}_6\text{H}_4\text{Z})\text{Cl}(\text{dppe})_2]^+$ as their BPh_4^- salts (equation I):-



6 Z = CH_3 , 60 %, violet

7 Z = Br, 64 %, maroon

8 Z = Cl, 64 %, maroon

These complexes 6, 7, and 8 are all air-stable darkly coloured cationic Tc^{IV} -imido complexes. Chromatographic analysis (HPLC, beta detection) indicates single ^{99}Tc -containing species. They are quite soluble in CH_2Cl_2 and insoluble in ether, petrol and alcohols. They may be conveniently recrystallised from $\text{CH}_2\text{Cl}_2/\text{MeOH}$.

Their assignment as $\text{Tc}(\text{IV})$ complexes is from the following characterisation: The analysis stoichiometry fits the formula $[\text{Tc}(\text{NR})\text{Cl}(\text{dppe})_2](\text{BPh}_4)$. Although $\gamma \text{ Tc}=\text{N}$ is not assignable there is no evidence for $\gamma \text{ NH}$ in the infrared. The compounds exhibit very broadened NMR spectra (^1H , ^{31}P) at room temperature which are not easily assigned. They are assumed to be paramagnetic Tc^{IV} imido complexes and not Tc^{III} -amido (TcNHR) complexes on this basis.

This represents another new core, the $[\text{Tc}^{\text{IV}}=\text{NR}]^{2+}$ moiety. Evidence for the existence of this new Tc^{IV} core comes from the structural characterisation of a $[\text{Tc}^{\text{IV}}\text{-hydrazido}(2\text{-})\text{bis}(\text{dppe})\text{Cl}]^+$ cation which contains a $[\text{Tc}^{\text{IV}}\text{NNR}_2]^{2+}$ core¹⁸. Hydrazido(2-) and imido(2-) are formally analogous. Further evidence comes from the existence and relative stability of the analogous $[\text{Tc}^{\text{IV}}=\text{O}]^{2+}$ core from the electrochemical reduction of some Tc^{V} oxo Schiff base complexes¹⁹.

It is to be understood that reactions of the aforementioned type A-F are well known for the synthesis of various transition metal hydrazido (2-) and imido complexes^{3,10}. While it is believed that they have not previously been used for the production of technetium complexes of the kind described and claimed herein, it is acknowledged that the synthesis of technetium-nitride complexes using hydrazine hydrochloride itself has already been reported^{15,16}.

Using the approach of equation A above, the reactions of hydrazines with $[\text{NBu}_4][\text{TcOCl}_4]$ were studied, and the intermediate products further functionalised with mono- or bi-dentate ligands. In particular, the reaction of complexes containing technetium-oxo moieties $[\text{Tc}=\text{O}]$ with mono-substituted hydrazines or 1,1-disubstituted hydrazines produces technetium-diazenide or technetium-hydrazide (2-) species.

The facile synthesis of $[\text{TcCl}(\text{NNPh})_2(\text{PPh}_3)_2]$ from $[\text{Bu}_4\text{N}][\text{TcOCl}_4]$, PhNHNH_2 , and PPh_3 in methanol under reflux has been demonstrated.²⁵ This complex proved to be somewhat insoluble and could not be satisfactorily recrystallised due to its poor solubility. This unsubstituted phenyl-diazenido-complex thus appears to be polymeric, possibly containing chloro- bridges. Consequently it was not thought to be a

suitable starting material for investigation of substitution chemistry.

Use of 4-substituted hydrazine hydrochlorides $4\text{-XC}_6\text{H}_4\text{NHNH}_2\cdot\text{HCl}$ ($\text{X} = \text{Cl}, \text{CH}_3$) has led to the preparation of the analogous bisdiazenido- complexes $[\text{TcCl}(\text{NNC}_6\text{H}_4\text{X})_2(\text{PPh}_3)_2]$ ($\text{X} = \text{Cl}, \underline{9}$; $\text{X} = \text{CH}_3, \underline{10}$). These air-stable orange crystalline solids are reasonably soluble compounds and are much superior starting materials. Complex 9 ($\text{X} = \text{Cl}$) in particular has proved to be the most suitable for a systematic investigation of the substitution chemistry of the technetium bis diazenido- complexes, giving relatively clean products on reaction with the appropriate ligand.

A most important development in this work is the fact that these diazenido- complexes $[\text{TcCl}(\text{NNR})_2(\text{PPh}_3)_2]$ may also be synthesised directly from $[\text{TcO}_4]^-$. Reaction of $[\text{NH}_4][\text{TcO}_4]$ with $\text{ClC}_6\text{H}_4\text{NHNH}_2\cdot\text{HCl}$ and PPh_3 in dry methanol under reflux gives a good (60-70%) yield of $[\text{TcCl}(\text{NNC}_6\text{H}_4\text{Cl})_2(\text{PPh}_3)_2]$ 9. Many variations in experimental conditions were tried. The best method is reported here. This result suggests that all technetium diazenido- complexes may be synthesised in good yield directly from $[\text{TcO}_4]^-$.

In order to investigate which complexes could be synthesised directly from $[\text{TcO}_4]^-$ in future work, it has been important to demonstrate that the diazenido- (and imido-) cores may be incorporated into a wide variety of complex types. For diazenido- cores this has mainly been approached by the systematic substitution of 9.

Reaction of 9 with excess dppe in methanol under reflux gives pure $[\text{TcCl}(\text{NNC}_6\text{H}_4\text{Cl})(\text{dppe})_2]^+$, 12 isolated as orange crystalline BPh_4^- or PF_6^- salts in good yield. Complexes of this type may also be prepared directly from $[\text{NH}_4][\text{TcO}_4]$.

Reaction of 9 with dmpe under similar conditions leads to the isolation of a pale-pink cationic solid (HPLC retention time 10 minutes, single species) containing no nitrogen. This product could not be isolated in pure form, but is tentatively formulated as $[\text{Tc}(\text{dmpe})_3][\text{BPh}_4]$. The analogous reaction under less forcing conditions at room temperature leads to the desired cation $[\text{TcCl}(\text{NNC}_6\text{H}_4\text{Cl})(\text{dmpe})_2]^+$ isolated as its PF_6^- salt (HPLC retention time 9.6 minutes, single species).

In order to elucidate the validity of both $[\text{Tc}(\text{N}_2\text{Ar})_2]^+$ and $[\text{Tc}(\text{N}_2\text{Ar})]^{2+}$ as new cores for the development of Tc-based radiopharmaceutical products it was necessary to investigate the lability of the $-\text{N}_2\text{Ar}$ unit on reaction with other ligands. Detailed HPLC experiments (beta detection) were performed to see if a bis diazenido- intermediate was formed in the preparation of the cation 12 (retention time 14 minutes) from the starting material 9 (retention time 9.4 minutes). The HPLC results showed that the cation formed after only 15 minutes stirring at room temperature, and that no other Tc-containing intermediate was detected. This proves that one $-\text{N}_2\text{Ar}$ moiety is very labile, and is easily lost in solution at room temperature in the presence of the appropriate ligand to give the monodiazenido- product.

Reaction of 9 and 10 with the less bulky phosphines (PMe_2Ph , PMePh_2) gave single species in solution (HPLC). However, the high solubility precluded further workup of these apparently cationic products. Reaction of $[\text{Bu}_4\text{N}][\text{TcOCl}_4]$, $\text{XC}_6\text{H}_4\text{NHNH}_2\cdot\text{HCl}$ ($\text{X} = \text{Cl}, \text{CH}_3$) and the appropriate phosphine also leads to isolation of these solutions (HPLC).

Reaction of the commercially available hydrazine $\text{O}_2\text{NC}_6\text{H}_4\text{NHNH}_2$ with $[\text{Bu}_4\text{N}][\text{TcOCl}_4]$ and PPh_3 in methanol leads to the isolation of the lime-green Tc(III) monodiazenido-complex $[\text{TcCl}_2(\text{NNC}_6\text{H}_4\text{NO}_2)(\text{PPh}_3)_2]$, 11 in reasonable yield. Apparently a bis diazenido- complex is not formed from reaction of this nitro-substituted phenylhydrazine. The complex 11 promises to be a useful starting material for the preparation of a variety of monodiazenido- complexes as it has two easily replaceable chlorides. In the presence of dppe in methanol-toluene under reflux complex 11 gives orange $[\text{TcCl}(\text{NNC}_6\text{H}_4\text{NO}_2)(\text{dppe})_2]^+$, 13 isolated as its BPh_4^- salt in good yield. $[\text{TcCl}(\text{NNC}_6\text{H}_4\text{NO}_2)(\text{dmpe})_2][\text{PF}_6]$ (retention time 10 minutes, single species) was prepared in high yield directly from $[\text{TcOCl}_4]^-$, the hydrazine, and dmpe in refluxing methanol-toluene.

Reaction of 9 with sodium dimethyldithiocarbamate in absolute ethanol under reflux gives the novel orange Tc(III) diazenido- complex $[\text{Tc}(\text{NNC}_6\text{H}_4\text{Cl})(\text{S}_2\text{CNMe}_2)_2(\text{PPh}_3)]$, 14 in reasonable (66%) yield. Complex 14 is air-stable both in the solid state and in solution. Recrystallisation from $\text{CH}_2\text{Cl}_2/\text{Et}_2\text{O}$ gives X-ray quality orange crystals. Satisfactory elemental analysis and spectroscopic data suggest the formulation to be correct. The room temperature ^1H NMR spectrum of 14 is indicative of its coordination geometry. The four methyl groups in 14 appear as four sharp singlets. This resonance pattern shows that the two dithiocarbamate ligands are non-equivalent, and is consistent with a *cis*-conformation. This has to be confirmed by X-ray structure analysis. If the dithiocarbamate ligands were *trans*- and the four methyl groups thus equivalent, the ^1H spectrum would show a single resonance which would not be expected to change with temperature.

Reaction of 9 with maltol gives a dark-orange crystalline compound. This is a single species (HPLC) and analyses as $[\text{TcCl}(\text{NNC}_6\text{H}_4\text{Cl})(\text{maltol})(\text{PPh}_3)_2]$, 15. This novel Tc(III) diazenido complex is formally analogous to the structurally characterised $[\text{ReCl}(\text{NNCOPh})(\text{maltol})(\text{PPh}_3)_2]^{2+}$, and is the first reported Tc

complex containing the maltol ligand.

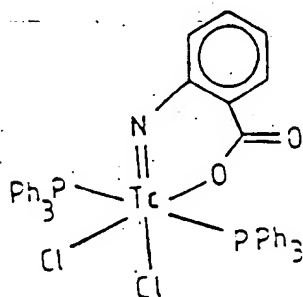
Reaction of 9 with the tetradentate $N_2O_2(2-)$ ligand $salenH_2$ in methanol-toluene under reflux in the presence of Et_3N gives the neutral dark-green Tc(III) diazenido- complex $[Tc(NNC_6H_4Cl)(salen)(PPh_3)]$, 16 in good yield. Similar reaction of 9 with the obligately planar tetradentate $N_2O_2(2-)$ ligand $salphenH_2$ gave no well defined product suggesting that a *cis*-geometry of the $-N_2Ar$ and PPh_3 groups is preferred. Further evidence for a preferred *cis*-geometry is suggested from the spectroscopic results of 14. This is expected to be confirmed by X-ray structure analysis.

Reaction of 9 with the N_2S_2 ligand $(HSCH(Me)CONHCH_2-)_2$ in the presence of Et_3N gave a dark-brown solid. The product was too insoluble for satisfactory analysis by NMR, but appeared to be diamagnetic. Elemental analysis on the product isolated directly from the reaction mixture suggested the formulation as a bis diazenido- complex $[Tc(NNC_6H_4Cl)_2-(SCH(Me)CONHCH_2CH_2NHCOCH(Me)S)]_x$, 17.

Much effort has been directed to the development of a synthetic route to Tc imido- complexes directly from $[TcO_4]^-$. Reaction of aqueous methanolic solutions of $[TcO_4]^-$ with aromatic amine and PPh_3 in the presence of concentrated HCl gives only low yields of the desired Tc(V) imido- complexes $[TcCl_3(NAr)(PPh_3)_2]$. These complexes have been prepared previously from $[Bu_4N][TcOCl_4]$.²⁵ The nature of the reaction from $[TcO_4]^-$ appears to be very dependent on the concentration of HCl used. Use of excess HCl gives $[TcCl_4(PPh_3)_2]$.

The use of amine hydrochloride ($ArNH_3Cl$) as an alternative to the addition of HCl in this reaction has also been investigated in some detail. $[TcO_4]^-$ reacts with $ArNH_3Cl$ and PPh_3 in aqueous methanol to give a bright blue, neutral product in high yield after about 20 minutes stirring at room temperature. This product appears to be independent of the aromatic amine hydrochloride used. The blue compound appears to be diamagnetic (NMR) and shows evidence for coordinated PPh_3 , but contains no nitrogen. This compound analyses reasonably as $[Tc_2Cl_4(PPh_3)_4]$ which is analogous to many known Re-Re multiply bonded species. Use of aliphatic amine hydrochlorides (RNH_3Cl) leads to rapid conversion to black insoluble " $TcO_2 \cdot xH_2O$ ".

Reaction of $[NH_4][TcO_4]$ with the hydrochloride of anthranilic acid ($2-HO_2C_6H_4NH_3Cl$) under analogous conditions gives a lime-green precipitate. This analyses reasonably well as $[TcCl_2(NC_6H_4CO_2)(PPh_3)_2]$, 18 and is expected to have the novel structure containing a bent TcNC framework. The bent chelating imidobenzoate(3-) ligand is thus a new core moiety for technetium. The complex 18 may also be prepared from $[TcOCl_4]^-$ in lower yield. Anthranilic acid is known to react with $[ReOCl_3(PPh_3)_2]$ in ethanol to give the chelating imidobenzoate(3-) complex $(ReCl(OEt)(NC_6H_4CO_2)(PPh_3)_2)$.²⁷

18

This is a major development as it suggests that imido- complexes are more generally accessible from $[TcO_4]^-$. The chelate effect must in some way stabilise the formation of this imido- ligand. The establishment of a conjugation pathway through the $M=N$, $C=C$, and $C=O$ may be a driving force for its formation. The reaction of $[TcO_4]^-$ and anthranilic acid hydrochloride in the presence of a wide variety of non-phosphine ligands is envisaged.

Much effort has been directed to synthesis of Tc imido- ligands from $[TcO_4]^-$ using the hydrazines $RCONHNHAr$ ($R = CH_3, Ph$), and also their hydrochlorides as a source of the NAr ligand. Use of the symmetrically substituted hydrazines $RNHNHR$ ($R = Me, Et, PhCO, Ph$) is also envisaged. Preliminary experiments for both $[TcO_4]^-$ and $[TcOCl_4]^-$ have shown that mixtures of products are being formed (HPLC).

Our work has resulted in the synthesis of two new classes of technetium complexes with hydrazido (2-), i.e. $=NNR_2$, and diazenido, i.e. $-NNR$, substituents, at both the carrier added (^{99}Tc) and the no carrier added (^{99m}Tc) levels. Both neutral and cationic derivatives have been prepared within each class. These

complexes are useful as radiopharmaceuticals and thus provide a new range of such reagents.

Specifically, the following new complexes containing hydrazido (2-) and diazenido moieties have been prepared:-

⁹⁹Tc: Carrier Added Level

- 5 [Tc^V(NNMePh)Cl₃(PPh₃)₂]
 [Tc^V(NNMePh)Cl₂(PMe₂Ph)₃][PF₆]
 [Tc^V(NNMePh)Cl(Et₂NCS₂)₂]
 [Tc(N₂)Cl(dppe)₂]
 [Tc^{IV}(NNMe₂)Cl(dppe)₂][PF₆]
 10 [Tc^VO(NH)dppe][PF₆]
 [Tc^{III}(NNPh)₂Cl(PPh₃)₂]
 [Tc^{III}(NNPh)Cl(dppe)₂][PF₆]
 [Tc(NNC₆H₄Cl)Cl(dppe)₂][PF₆]
 [Bu₄N][Tc(NC₆H₄CH₃)Br₄], [Bu₄N][Tc(NC₆H₄CH₃)Cl₄], Tc
 15 (NC₆H₄Z)Cl₃(PPh₃)₂ where Z = CH₃, Br, Cl,
 [Tc(NC₆H₄Z)Cl(dppe)₂][BPh₄], where Z is as above.

^{99m}Tc: No-Carrier Added Level*

- [Tc^{III}(NNPh)Cl(L)₂]⁺ [Tc^{III}(NNPh)Cl(L)₂]⁺
 L =
 20 dmpe, dppe, P46, P53, P56, P68, PL28, PL31, PL34, PL37, PL38, PL40, PL42, PL43, PL46,
 PL49, PL50.
 [Tc^{III}(NNC₆H₄NO₂)Cl(L)₂]⁺
 L = dmpe
 [Tc^{IV}(NNMePh)Cl(L)₂]⁺
 L = dmpe, P34, P46, P53, P65, P68, PL28, PL38

25 Of these, animal biodistribution data has been obtained for the following ^{99m}Tc species and the results are shown in Tables 2, 3 and 4:-

- [Tc^{III}(NNPh)Cl(L)₂]⁺
 L = dmpe, PL28, P46, PL42, PL43, P65, PL50, PL38 (Table 2)
 [Tc^{III}(NNC₆H₄NO₂)Cl(L)₂]⁺
 30 L = dmpe (Table 3)
 [Tc^{IV}(NNMePh)Cl(L)₂]⁺
 L = dmpe, P46, P65 (Table 4)

This invention will now be further illustrated by the following Examples:-

35 ⁹⁹Tc Complexes

All reactions were performed under an atmosphere of nitrogen using predried, distilled solvents unless noted otherwise. [NBu₄][TcOCl] was prepared by the literature procedure²⁰. All other reagents used were obtained from commercial sources and used as received. Aqueous solutions of [NH₄][TcO₄] were obtained from Amersham International plc.

40 All complexes were characterised by elemental analysis, IR, ¹H NMR and ³¹P NMR. Only analytical data are included here but spectroscopic information is available. In addition to the above physical characterisation of the complexes single crystal X-ray structures have been obtained for four complexes: [Tc(NNPh)Cl(dppe)₂][PF₆], [Tc(NH)O(dppe)₂][PF₆], [Tc(NNMe₂)Cl(dppe)₂][PF₆] and Tc(NC₆H₄CH₃)Cl₃(PPh₃)₂.

45 Example 1

Reaction of (Bu₄N)[TcOX₄] (X = Cl, Br) with 4-Tolyl-isocyanate

50 i) Tetrabutylammonium(1+)tetrachloro(p-tolylimido) technetate (V) (1-), (Bu₄N)[Tc(Ntol)Cl₄]

(Bu₄N)[TcOCl₄] (0.194 g, 0.39 mmol) was suspended in dry degassed toluene (10 ml) and MePhNCO (0.25 ml, 1.98 mmol, 5 equivalents) was added. The mixture was then vigorously refluxed under N₂ for 45 minutes. After cooling to room temperature the toluene was decanted off, and the black residue was
 55 triturated with dry diethyl ether (10 ml) before collection of the blue-black solid 1 by filtration. On washing thoroughly with diethyl ether the product was dried in vacuo. (Yield 0.229 g, 0.39 mmol, 100%). In similar

* The structures of the ligands, L, given here are shown in Table 1.

preparations of 1 the yield was never less than 95% and therefore the conversion was considered to be essentially quantitative. (Found: C, 49.31; H, 7.22; N, 5.02. calc for $\text{TcC}_{23}\text{H}_{43}\text{N}_2\text{Cl}_4$: C, 47.03; H, 7.37; N, 4.77%); ^1H NMR (d_6 -DMSO) 0.9[12H, broad unresolved triplet, $(\text{CH}_3(\text{CH}_2)_3)_4\text{N}$]; 1.4[24H, broad multiplet, $(\text{CH}_3(\text{CH}_2)_3)_4\text{N}$]; 2.2[3H, singlet, $\text{CH}_3\text{C}_6\text{H}_4\text{N-Tc}$]; 7.0-7.4[4H, multiplet, $\text{CH}_3\text{C}_6\text{H}_4\text{NTc}$]; ν_{max} . (Nujol mull, KBr plates) 1170 cm^{-1} (Tc = N, tentative assignment).

ii) Tetrabutylammonium(1+)tetrabromo(p-tolylimido) technetate (V) (1-), $(\text{Bu}_4\text{N})[\text{Tc}(\text{Ntol})\text{Br}_4]$ 2

The blue-black product 2 was prepared in a similar fashion to 1 using $(\text{Bu}_4\text{N})[\text{TcOBr}_4]$ (0.268 g, 0.396 mmol) and MePhNCO (0.25 ml, 1.98 mmol, 5 equivalents) in refluxing dry toluene (15 ml). (Yield 0.224 g, 0.29 mmol, 74%). HPLC retention time 9.6 minutes, single species; (Found: C, 36.73; H, 6.43; N, 3.16. calc for $\text{TcC}_{23}\text{H}_{43}\text{N}_2\text{Br}_4$: C, 36.10; H, 5.66; N, 3.66%); ^1H NMR (CDCl_3) 1.0[12H, broad unresolved triplet, $(\text{CH}_3(\text{CH}_2)_3)_4\text{N}$]; 1.5[24H, broad multiplet, $(\text{CH}_3(\text{CH}_2)_3)_4\text{N}$]; 2.27[3H, singlet, $\text{CH}_3\text{C}_6\text{H}_4\text{NTc}$]; 6.9-7.5[4H, multiplet, $\text{CH}_3\text{C}_6\text{H}_4\text{NTc}$]; ν_{max} . (Nujol mull, KBr plates) 1175 cm^{-1} (Tc = N, tentative assignment).

Example 2

Reactions of $(\text{Bu}_4\text{N})[\text{TcOCl}_4]$ with Aromatic Amines. (4-ZC₆H₄NH₂, Z = CH₃, Br Cl) in the Presence of Triphenylphosphine, PPh₃

i) Trichloro(p-tolylimido)bis(triphenylphosphine) technetium (V), $\text{Tc}(\text{NC}_6\text{H}_4\text{Z})\text{Cl}_3(\text{PPh}_3)_2$ Z = CH₃, 3

$(\text{Bu}_4\text{N})[\text{TcOCl}_4]$ (0.216 g, 0.43 mmol), $\text{CH}_3\text{C}_6\text{H}_4\text{NH}_2$ (0.07 g, 0.65 mmol, 1.5 equivalents) and PPh₃ - (0.34 g, 1.3 mmol, 3 equivalents) were refluxed in dry methanol (10 ml) under N₂ for 40 minutes. After cooling to room temperature, the brown-green mixture was evaporated to 5 ml, and diethyl ether (15 ml) was added to aid precipitation of 3. The green-brown product was collected by filtration, washed thoroughly with ether and dried. The product could be recrystallised from CH_2Cl_2 /hexane mixture. (Yield 0.094 g, 0.11 mmol, 26%). HPLC retention time 10.8 minutes, single species; (Found: C, 59.01; H, 4.35; N, 1.76; Cl, 12.80. calc for $\text{TcC}_{43}\text{H}_{37}\text{NCl}_3\text{P}_2$: C, 61.84; H, 4.46; N, 1.68; Cl, 12.74%); ^1H NMR (CDCl_3) 2.2[3H, s, $\text{CH}_3\text{C}_6\text{H}_4\text{NTc}$]; 6.5-6.8[4H, m, $\text{CH}_3\text{C}_6\text{H}_4\text{NTc}$]; 7.0-8.0[30H, m, phenyl H]. There was no evidence of NH in the proton spectrum; ^{31}P - $\{^1\text{H}\}$ NMR (CDCl_3) 30.02 s ppm; ν_{max} . (Nujol mull, KBr plates) 1165 cm^{-1} (Tc = N, tentative assignment). There were no absorptions which could be attributed to ^vNH .

ii) Trichloro(p-bromophenylimido)bis(triphenylphosphine) technetium (V), $\text{Tc}(\text{NC}_6\text{H}_4\text{Z})\text{Cl}_3(\text{PPh}_3)_2$ Z = Br, 4

$(\text{Bu}_4\text{N})[\text{TcOCl}_4]$ (0.210 g, 0.42 mmol), $\text{BrC}_6\text{H}_4\text{NH}_2$ (0.11 g, 0.64 mmol, 1.5 equivalents) and PPh₃ - (0.331 g, 1.26 mmol, 3 equivalents) were refluxed in dry methanol (10 ml) to give on workup and recrystallisation from CH_2Cl_2 /hexane a very low yield of brown solid 4. (Yield 0.052 g, 0.06 mmol, 14%). HPLC retention time 9.6 minutes, single species; (Found: C, 54.38; H, 4.00; N, 1.53; Cl, 10.56. calc for $\text{TcC}_{42}\text{H}_{34}\text{NP}_2\text{Cl}_3\text{Br}$: C, 56.05; H, 3.81; N, 1.56; Cl, 11.82. calc for $\text{TcC}_{42}\text{H}_{34}\text{NP}_2\text{Cl}_3\text{Br} \cdot 1/2 \text{CH}_2\text{Cl}_2$: C, 54.45; H, 3.72; N, 1.48; Cl, 14.95%); ^1H NMR (CDCl_3) 5.25[s, CH_2Cl_2]; 6.8[4H, m, $\text{BrC}_6\text{H}_4\text{NTc}$]; 7.0-8.0[30H, m, phenyl H]; ^{31}P - $\{^1\text{H}\}$ NMR (CDCl_3) 29.93 s ppm; ν_{max} . (Nujol mull, KBr plates) 1165 cm^{-1} (Tc = N, tentative assignment).

iii) Trichloro(p-chlorophenylimido)bis(triphenylphosphine) technetium (V), $\text{Tc}(\text{NC}_6\text{H}_4\text{Z})\text{Cl}_3(\text{PPh}_3)_2$ Z = Cl, 5

$(\text{Bu}_4\text{N})[\text{TcOCl}_4]$ (0.272 g, 0.545 mmol), $\text{ClC}_6\text{H}_4\text{NH}_2$ (0.104 g, 0.82 mmol, 1.5 equivalents) and PPh₃ - (0.43 g, 1.64 mmol, 3 equivalents) were refluxed in dry methanol (10 ml) to give a very low yield of brown solid 5. (Yield 0.084 g, 0.098 mmol, 18%). HPLC retention time 9.2 minutes, single species; (Found: C, 55.85; H, 3.86; N, 1.63. calc for $\text{TcC}_{42}\text{H}_{34}\text{NP}_2\text{Cl}_4$: C, 58.96; H, 4.00; N, 1.64%); ^1H NMR (CDCl_3) 6.5-6.7[4H, m, $\text{ClC}_6\text{H}_4\text{NTc}$]; 7.0-8.0[30H, m, phenyl H]; ^{31}P - $\{^1\text{H}\}$ NMR (CDCl_3) 29.87 s ppm; ν_{max} . (Nujol mull, KBr plates) 1170 cm^{-1} (Tc = N, tentative assignment).

Example 3

Reactions of $(\text{Bu}_4\text{N})[\text{TcOCl}_4]$ with Aromatic Amines ($4\text{-ZC}_6\text{H}_4\text{NH}_2$, $\text{Z} = \text{CH}_3, \text{Br}, \text{Cl}$) in the Presence of Bis-(diphenylphosphino)ethane, dppe

i) $[\text{Tc}(\text{NC}_6\text{H}_4\text{Z})\text{Cl}(\text{dppe})_2](\text{BPh}_4)\text{Z} = \text{CH}_3$, 6

$(\text{Bu}_4\text{N})[\text{TcOCl}_4]$ (0.333 g, 0.67 mmol), $\text{CH}_3\text{C}_6\text{H}_4\text{NH}_2$ (0.36 g, 3.33 mmol, 5 equivalents), and dppe (0.80 g, 2.0 mmol, 3 equivalents) in dry degassed methanol (20 ml) were refluxed for 1 hour. After cooling to room temperature, the violet mixture was filtered into a clean flask to remove some insoluble red material. Sodium tetraphenylborate (0.23 g, 0.67 mmol) in methanol (5 ml) was added with stirring to immediately precipitate out a copious amount of violet solid 6. The product was collected by filtration and washed thoroughly with MeOH, and then ether. The product could be recrystallised from $\text{CH}_2\text{Cl}_2/\text{MeOH}$ or $\text{CH}_2\text{Cl}_2/\text{hexane}$. (Yield 0.544 g, 0.40 mmol, 60%). HPLC retention time 8.4 minutes, one major species; (Found: C, 74.09; H, 7.09; N, 1.70; Cl, 3.22. calc for $\text{TcC}_{83}\text{H}_{75}\text{NCIP}_4\text{B}$: C, 73.54; H, 5.58; N, 1.03; Cl, 2.62%).

There are no infrared absorptions assignable to NH stretches, and the $\nu_{\text{Tc}=\text{N}}$ stretch could not be assigned unambiguously. The product gave a broadened ^1H NMR spectrum and was assumed to be paramagnetic $\text{Tc}(\text{IV})$. The ^{31}P NMR spectrum also showed broadened resonances.

If less ArNH_2 was used in the reaction a red precipitate believed to be $[\text{Tc}^{\text{III}}\text{Cl}_2(\text{dppe})_2]\text{Cl}$ forms in approximately 50% yield from the MeOH on cooling to room temperature.

ii) $[\text{Tc}(\text{NC}_6\text{H}_4\text{Z})\text{Cl}(\text{dppe})_2](\text{BPh}_4)\text{Z} = \text{Br}$, 7

$(\text{Bu}_4\text{N})[\text{TcOCl}_4]$ (0.179 g, 0.36 mmol), $\text{BrC}_6\text{H}_4\text{NH}_2$ (0.31 g, 1.79 mmol, 5 equivalents) and dppe (0.429 g, 1.08 mmol, 3 equivalents) were refluxed in dry methanol (10 ml, 1 hour). NaBPh_4 (0.122 g, 0.36 mmol) in MeOH (5 ml) was added to the cooled filtered reaction mixture with stirring to isolate 7 as a maroon solid on filtration. (Yield 0.325 g, 0.23 mmol, 64%). HPLC retention time 7.6 minutes, one major species. Analysis on the crude material gave (Found: C, 73.19; H, 5.91; N, 0.89; Cl, 3.19. calc for $\text{TcC}_{82}\text{H}_{72}\text{NBrClP}_4\text{B}$: C, 69.33; H, 5.11; N, 0.99; Cl, 2.50%) and suggests contamination with BPh_4^- or Cl^- . The product could be recrystallised from $\text{CH}_2\text{Cl}_2/\text{MeOH}$.

iii) $[\text{Tc}(\text{NC}_6\text{H}_4\text{Z})\text{Cl}(\text{dppe})_2](\text{BPh}_4)\text{Z} = \text{Cl}$, 8

$(\text{Bu}_4\text{N})[\text{TcOCl}_4]$ (0.28 g, 0.56 mmol), $\text{ClC}_6\text{H}_4\text{NH}_2$ (0.358g, 2.8 mmol, 5 equivalents) and dppe (0.67 g, 1.68 mmol, 3 equivalents) were refluxed in dry methanol (15 ml, 75 minutes). NaBPh_4 (0.19 g, 0.56 mmol) in MeOH (5 ml) was added to the cooled filtered reaction mixture with stirring to precipitate out the dark maroon solid 8 which was collected by filtration. (Yield 0.497 g, 0.36 mmol, 64%). HPLC retention time 8.0 minutes, one major species. Analysis on the crude material gave (Found: C, 73.56; H, 5.94; N, 1.72; Cl, 3.26. calc for $\text{TcC}_{82}\text{H}_{72}\text{NCl}_2\text{P}_4\text{B}$: C, 71.57; H, 5.27; N, 1.02; Cl, 5.15%) and suggests contamination with BPh_4^- . The product could be recrystallised from $\text{CH}_2\text{Cl}_2/\text{MeOH}$.

Example 4

The preparation of $(\text{Tc}(\text{NNPh})_2\text{Cl}(\text{PPh}_3)_2)$

Dry, distilled MeOH (5 cm^3) was added to a reaction flask containing a magnetic stirring bar, 222 mg PPh_3 (0.85 mmol) and 70 mg $[\text{NBu}_4][\text{TcOCl}_4]$ (0.14 mmol). This gave an orange suspension containing undissolved PPh_3 . After five minutes 0.60 cm^3 of PhHNHNH_2 (6.1 mmol) was added and the reaction mixture was heated to reflux for one hour. The solution was cooled to room temperature overnight and the resultant yellow-gold precipitate was collected, washed with MeOH (5 cm^3) and Et_2O (10 cm^3). The yield of $\text{Tc}(\text{NNPh})_2\text{Cl}(\text{PPh}_3)_2$, after drying in *vacuo*, was 94 mg (0.11 mmol, 80%) based on technetium. This material is only partially soluble in halogenated solvents and insoluble in alcohols. Hence, attempts to purify the complex were only partially successful. Analysis calculated for $\text{C}_{48}\text{H}_{40}\text{ClN}_4\text{P}_2\text{Tc}$: 66.32% C; 4.64% H; 6.45% N. Found: 64.23% C; 4.28% H; 4.87% N.

Example 5The preparation of $[\text{Tc}(\text{NNPh})\text{Cl}(\text{dppe})_2][\text{PF}_6]$ 5 Method 1

52 μl of PhNHNH_2 (0.53 mmol) was added to a stirred solution of 80 mg $[\text{NBu}_4][\text{TcOCl}_4]$ (0.16 mmol) in 5 cm^3 MeOH. After five minutes 253 mg of dppe (0.64 mmol) was added as a solid to the stirred reaction mixture and this was then heated to reflux for one hour. The solution was cooled to room temperature, 10 filtered, and an excess of NH_4PF_6 (1 g) in 3 cm^3 water was added to precipitate an orange compound. This was collected, washed with MeOH (15 cm^3) and Et_2O (30 cm^3), and dried in the air. This gave 95 mg of product (0.08 mmol, 50%). The complex could be recrystallised from $\text{CH}_2\text{Cl}_2/\text{EtOH}$. Analysis calculated for $\text{C}_{58}\text{H}_{53}\text{ClF}_6\text{N}_2\text{P}_5\text{Tc}$: 58.97% C; 4.61% H; 2.37% N. Found: 58.92% C; 4.68% H; 2.70% N.

15 Method 2

A methanolic solution of $[\text{NH}_4][\text{TcO}_4]$ was prepared by adding 0.50 cm^3 of a 0.29 M aqueous solution of $[\text{NH}_4][\text{TcO}_4]$ (0.15 mmol) to 3.0 cm^3 of reagent grade MeOH. Phenyl hydrazine (50 μl , 0.51 mmol) was then added to this stirred solution. No reaction appeared to take place until 0.1 cm^3 of concentrated HCl was 20 added to the reaction mixture five minutes later. This was immediately followed by the addition of 241 mg dppe (0.81 mmol) as a solid. The reaction mixture was heated to reflux for one hour, cooled to room temperature and filtered to remove excess, unreacted dppe. An excess of $[\text{NH}_4][\text{PF}_6]$ was added to the stirred solution as a solid and the resultant suspension was stirred at room temperature overnight. The orange precipitate was then collected, washed with $^i\text{PrOH}$ and Et_2O and dried in vacuo to give 108 mg of 25 $[\text{Tc}(\text{NNPh})(\text{dppe})_2\text{Cl}][\text{PF}_6]$ (0.09 mmol, 60%). The product was identified by comparison of its IR and ^1H NMR spectra with those obtained from an authentic sample prepared by Method 1.

Example 630 The Preparation of $[\text{Tc}(\text{NNC}_6\text{H}_4\text{Cl})(\text{dppe})_2\text{Cl}][\text{PF}_6]$

This complex was prepared according to Method 2 above from $[\text{NH}_4][\text{TcO}_4]$ (0.19 mmol), 129 mg trans- $\text{ClC}_6\text{H}_4\text{NHNH}_2\cdot\text{HCl}$ (1.07 mmol), 0.1 cm^3 concentrated HCl, and 561 mg dppe (1.41 mmol). Yield of $[\text{Tc}(\text{NNC}_6\text{H}_4\text{Cl})(\text{dppe})_2\text{Cl}][\text{PF}_6]$: 298 mg, 0.24 mmol, 84%. Analysis calculated for $\text{C}_{58}\text{H}_{52}\text{Cl}_2\text{F}_6\text{N}_2\text{P}_5\text{Tc}$: 55.99% C; 4.25% H; 2.23% N. Found: 55.73% C; 4.37% H; 1.93% N. 35

Example 7The reaction of $[\text{NBu}_4][\text{TcOCl}_4]$ with Benzoylhydrazine and PPh_3

40 This reaction was performed according to the Method 1 above for the synthesis of $\text{Tc}(\text{NNPh})_2\text{Cl}(\text{PPh}_3)_2$ using 77 mg $[\text{NBu}_4][\text{TcOCl}_4]$, 70 mg PhC(O)NHNH_2 (0.51 mmol) and 135 mg PPh_3 (0.51 mmol). After the reaction solution had been heated to reflux for one hour and cooled to room temperature, a light orange compound precipitated and was collected, washed with MeOH (15 cm^3) and Et_2O (30 cm^3) and then dried 45 in the air. The compound was identified as $\text{TcNCl}_2(\text{PPh}_3)_2$ by comparison of its IR and NMR spectroscopic characteristics with those of an authentic sample.⁸ The yield was 97 mg (0.14 mmol, 88%). Analysis calculated for $\text{C}_{36}\text{H}_{30}\text{Cl}_2\text{NP}_2\text{Tc}$: 61.12% C; 4.27% H; 1.98% N. Found: 60.66% C; 4.35% H; 2.32% N.

Example 850 The reaction between $[\text{NBu}_4][\text{TcOCl}_4]$, Benzoylhydrazine and dppe

This reaction was performed according to Method 1 above using 119 mg $[\text{NBu}_4][\text{TcOCl}_4]$ (0.24 mmol), 91 mg PhC(O)NHNH_2 (0.67 mmol), and 323 mg dppe (0.81 mmol). The cooled reaction solution was filtered 55 and an excess of $[\text{NH}_4][\text{PF}_6]$ was added with stirring. The orange complex was identified as $[\text{TcN}(\text{dppe})_2\text{Cl}][\text{PF}_6]$ by comparison of its spectroscopic properties with those of an authentic sample.²¹ Yield: 196 mg (0.18 mmol, 75%). Analysis calculated for $\text{C}_{52}\text{H}_{48}\text{ClF}_6\text{NP}_5\text{Tc}$: 57.28% C; 4.44% H; 1.28% N. Found: 56.72% C; 4.84% H; 0.87% N.

Example 9The reaction between $[\text{NBu}_4][\text{TcOCl}_4]$, H_2NNH_2 and dppe

5 This reaction was performed by Method 1 above using 124 mg $[\text{NBu}_4][\text{TcOCl}_4]$ (0.25 mmol), 15 μl H_2NNH_2 (Aldrich, Anhydrous, 0.47 mmol) and 421 mg dppe (1.06 mmol). The reaction solution was heated to reflux for 30 minutes, cooled to room temperature, filtered and an excess of $[\text{NH}_4][\text{PF}_6]$ was added to the filtrate with stirring. The resultant orange-brown compound was collected by filtration. Yield: 144 mg (0.20 mmol, 80%). This product was identified as the complex $[\text{TcN}(\text{dppe})_2\text{Cl}][\text{PF}_6]$.

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Example 10The Synthesis of $\text{TcNNPhMe}(\text{PPh}_3)_2\text{Cl}_3$

15 108 mg $[\text{NBu}_4][\text{TcOCl}_4]$ (0.22 mmol) was dissolved in 10 cm^3 dry MeOH and 52 μl MePhNNH₂ (0.44 mmol) was added to the stirred solution. The solution changed from pale green to red-orange immediately. 211 mg PPh₃ (0.80 mmol) was added to the reaction solution and the resulting suspension was heated to reflux for one hour. The resulting suspension was cooled to room temperature and a large amount of a tan precipitate was collected, washed with MeOH (15 cm^3) and Et₂O (30 cm^3), and then dried *in vacuo*. The
20 yield was 108 mg of a complex identified as $[\text{Tc}(\text{NNPhMe})\text{Cl}_3(\text{PPh}_3)_2]$ (0.13 mmol, 59%). Analysis calculated for $\text{C}_{43}\text{H}_{38}\text{Cl}_3\text{N}_2\text{P}_2\text{Tc}$: 60.82% C; 4.51% H; 3.30% N; 12.53% Cl. Found: 60.01% C; 4.17% H; 3.53% N; 12.20% Cl.

Example 11

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The Preparation of $[\text{Tc}(\text{NNPhMe})\text{Cl}_2(\text{PMe}_2\text{Ph})_3][\text{PF}_6]$

A red-orange solution was prepared by adding 0.10 cm^3 MePhNNH₂ (0.85 mmol) to a stirred solution of 1.47 mg $[\text{NBu}_4][\text{TcOCl}_4]$ (0.30 mmol) in 4.0 cm^3 of MeOH. 0.20 cm^3 of PMe₂Ph was then added to the
30 reaction mixture and this was then heated to reflux for 45 minutes to give a clear orange solution. The solution was then concentrated to approximately 2 cm^3 and then 94 mg $[\text{NH}_4][\text{PF}_6]$ was added as a solid to the stirred reaction mixture. The precipitate which formed was collected and washed with 7:1 (v/v) Et₂O-¹PrOH. The filtrate was reconcentrated to give a second crop of gold-brown microcrystalline material. The
35 yield was 138 mg of $[\text{Tc}(\text{NNMePh})\text{Cl}_2(\text{PMe}_2\text{Ph})_3][\text{PF}_6]$ (0.16 mmol, 54%). Analysis calculated for $\text{C}_{31}\text{H}_{40}\text{Cl}_2\text{F}_6\text{N}_2\text{P}_4\text{Tc}$: 43.93% C; 4.76% H; 3.31% N. Found: 44.53% C; 5.22% H; 3.10% N.

Example 12The Preparation of $[\text{Tc}^{\text{V}}(\text{NNPhMe})\text{Cl}(\text{Et}_2\text{NCS}_2)_2]$

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A red-orange solution was prepared as described above from 138 mg $[\text{NBu}_4][\text{TcOCl}_4]$ (0.28 mmol) and 80 μl MePhNNH₂ (0.68 mmol) in 3 cm^3 of MeOH. After this solution had been stirred at room temperature for five minutes, a solution of 200 mg NaS₂CNEt₂·3H₂O (0.89 mmol) in 2 cm^3 MeOH. The resulting dark red
45 solution was heated to reflux for 30 minutes, cooled to room temperature and the solvent was removed *in vacuo* to give a red, oily residue. This residue was taken up in 5 cm^3 of ¹PrOH and this suspension was filtered to give 73 mg of a pale brown powder which was washed with Et₂O. The filtrate was concentrated to about 1-2 cm^3 volume and 50 cm^3 Et₂O was added. The precipitated thus formed was collected and identical to the original material isolated. The overall yield of the complex, identified as $[\text{Tc}(\text{NNMePh})\text{Cl}(\text{Et}_2\text{NCS}_2)_2]$ was 111 mg (0.02 mmol, 71%). The complex could be recrystallised from CH₂Cl₂/Et₂O.
50 Analysis calculated for $\text{C}_{17}\text{H}_{27}\text{ClN}_4\text{S}_4\text{Tc}$: 37.12% C; 4.95% H; 10.19% N; 6.44% Cl. Found: 38% C; 5% H; 11% N; 9.4% Cl.

Example 13The Reaction between $[\text{NBu}_4][\text{TcOCl}_4]$, MePhNNH₂ and dppe

55 An orange solution was prepared as described above from 100 mg $[\text{NBu}_4][\text{TcOCl}_4]$ (0.20 mmol), 45 μl MePhNNH₂ (0.38 mmol) in 4 cm^3 MeOH. 550 mg dppe (1.38 mmol) was then added to this stirred solution

as a solid and the resultant suspension was heated to reflux for one hour, cooled to room temperature and filtered to remove unreacted dppe. An excess of $[\text{NH}_4][\text{PF}_6]$ was added as a solid to the filtered solution to give a tan precipitate which was washed with MeOH (20 cm³) and Et₂O (10 cm³). This yielded 121 mg of $[\text{Tc}(\text{NH})\text{O}(\text{dppe})_2][\text{PF}_6]$ (0.11 mmol, 55%). Analysis calculated for C₅₂H₄₉F₆NOP₅Tc: 58.27% C; 4.61% H; 1.31% N. Found: 56.90% C; 4.70% H; 1.61% N.

Example 14

The Reaction of $[\text{NBu}_4][\text{TcOCl}_4]$, Me₂NNH₂ and dppe

Method 1

An orange-red solution was prepared as described above from 211 mg $[\text{NBu}_4][\text{TcOCl}_4]$ (0.42 mmol), 35 μl Me₂NNH₂ (0.46 mmol) in 5 cm³ MeOH and then 366 mg dppe (1.40 mmol) was added as a solid. The reaction mixture was heated to reflux for one hour, cooled to room temperature and a yellow precipitate was collected (72 mg of $[\text{Tc}(\text{N}_2)(\text{dppe})_2\text{Cl}]$ (0.07 mmol, 17%). An excess of $[\text{NH}_4][\text{PF}_6]$ was added as a solid to the filtrate to give a gold-brown precipitate (137 mg) of $[\text{Tc}(\text{NNMe}_2)\text{Cl}(\text{dppe})_2][\text{PF}_6]$ (0.12 mmol, 29%).

For $[\text{Tc}(\text{N}_2)(\text{dppe})_2\text{Cl}]$

Analysis calculated for C₅₂H₄₈ClN₂P₄Tc: 65.17% C; 5.05% H; 2.92% N. Found: 64.70% C; 5.32% H; 2.07% N.

For $[\text{Tc}(\text{NNMe}_2)\text{Cl}(\text{dppe})_2][\text{PF}_6]$

Analysis calculated for C₅₄H₅₂ClF₆P₅Tc: 57.33% C; 4.63% H; 2.48% N. Found: 51.6% C; 4.4% H; 1.8% N.

Method 2

A reaction solution was prepared as for Method 1 from 95 mg $[\text{NBu}_4][\text{TcOCl}_4]$ (0.19 mmol), 27 μl Me₂NNH₂ (0.36 mmol), 333 mg dppe (0.84 mmol) in 5 cm³ MeOH. This reaction mixture was stirred at room temperature for 70 hours. The reaction solution was filtered to remove excess dppe (no yellow precipitate was observed), 65 mg NH₄PF₆ (0.40 mmol) was added to the filtrate as a solid and the solution was then concentrated in vacuo and the residue was taken up in 5 cm³ CH₂Cl₂. This solution was filtered to remove undissolved inorganic salts. After filtration, 25 cm³ iPrOH was added to the filtrate to give 135 mg of a yellow-brown solid which was collected, washed and dried. This was identified by comparison of the IR spectrum of this complex with that of $[\text{Tc}(\text{NNMe}_2)\text{Cl}(\text{dppe})_2][\text{PF}_6]$ prepared by Method 1 (0.12 mmol, 63%).

Example 15

The Reaction of $[\text{NBu}_4][\text{TcOBr}_4]$, Me₂NNH₂ and dppe

This was performed by Method 1 for the reaction described above for $[\text{NBu}_4][\text{TcOCl}_4]$ using 130 mg $[\text{NBu}_4][\text{TcOBr}_4]$ (0.20 mmol), 20 μl Me₂NNH₂ (0.26 mmol), 247 mg dppe (0.62 mmol) in 5 cm³ MeOH. This gave 55 mg of a yellow complex, $\text{Tc}(\text{N}_2)\text{Br}(\text{dppe})_2$ (0.06 mmol, 30%). No salts were isolated from the reaction filtrate after the addition of an excess of NH₄PF₆ to the solution. Analysis calculated for C₅₂H₄₈BrN₂P₄Tc: 62.22% C; 4.82% H; 2.79% N. Found: 58.48% C; 4.71% H; 2.03% N.

^{99m}Tc Complexes

General: The ^{99m}Tc diazenide and hydrazide (2-) complexes were prepared in a straightforward fashion from the appropriate hydrazine, ^{99m}TcO₄⁻ and a suitable ligand. The complex preparations were found to yield the desired cationic products in reasonably high radiochemical purity (see Tables 2 - 4). The main contaminants in these preparations were the $(\text{Tc}^{\text{III}}\text{Cl}_2(\text{L})_2)^+$ cations, as verified by comparison of HPLC and TLC characteristics of these impurities with authentic samples of these Tc^{III} species prepared by a literature method.²² There is some question in the case of the MePhNNH₂ labelled species whether the complexes formed are of the formulation $[\text{Tc}^{\text{IV}}(\text{NNMeph})\text{Cl}(\text{L})_2]^+$ or $[\text{Tc}^{\text{V}}(\text{NH})\text{O}(\text{L})_2]^+$. Recent ICES studies on the preparation obtained from the labelling where L = P65 (mmmppe) have shown that the oxidation state of the

complex obtained is $+4$.²³ This indicates that the species present in the MePhNNH_2 preparations are the desired hydrazido (2-) species.

Reagents: The ligands used are given in Table 1. All other reagents used were from commercial suppliers and used as received. $[\text{}^{99\text{m}}\text{TcO}_4]^-$ was obtained as solutions in physiological saline from Amertec II generators. Reaction products were analyzed by HPLC, TLC and gel electrophoresis as described elsewhere.²⁴ All preparations were performed under an atmosphere of nitrogen gas.

Example 16

Complex Preparation: 20-25 μl of hydrazine was added to 2 cm^3 of absolute ethanol, then $^{99\text{m}}\text{TcO}_4^-$ (0.2 - 3.0 GBq) and 10mg of ligand were added to the solution. This mixture was heated to 120°C for 30 - 60 minutes, cooled to room temperature and analyzed. For biodistribution studies the total volume of the preparation was made up to 5 cm^3 by the addition of sterile saline solution.

Animal Biodistribution Studies: Six male Sprague Dawley rats were injected while under light ether anaesthesia with 0.1 cm^3 of preparation (i.v., tail vein) and half were sacrificed by cervical dislocation while under ether anaesthesia at the appropriate time interval post-injection and dissected. Organs were weighed and their activities measured in an ionisation chamber. For the purposes of calculations blood was assumed to constitute 5.8% of the total body weight, muscle was assumed to be 43% and the lungs were assumed to weigh 1g.

Biodistribution results are given in Tables 2 - 4.

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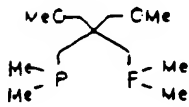
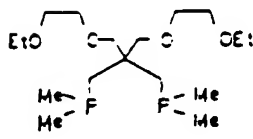
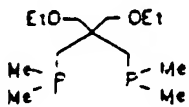
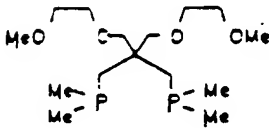
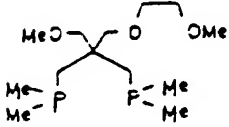
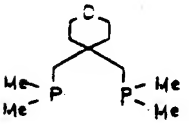
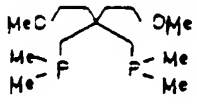
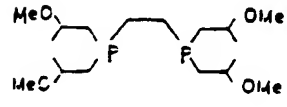
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Table 1: Ligands used in ^{99m}Tc labelling work

Abbreviation	Structure	Name
dmpe		1,2-bis(dimethylphosphino)ethane
dppe		1,2-bis(diphenylphosphino)ethane
P56		1,2-bis(di(3-methoxypropyl)phosphino)ethane
PL28		bis((dimethylphosphino)methyl)ether
P46		1,2-bis((2'-methoxy)ethoxymethyl)methylphosphino)ethane
PL34		1,3-bis(dimethylphosphino)-2-((2-methoxy)ethoxy)propane
PL38		1,3-bis(dimethylphosphino)-2,2-bis(2-(2-ethoxy)ethoxy)ethoxymethyl)propane; or 1,3-bis(dimethylphosphino)-2,2-bis(2,5,8-trioxadecyl)propane
PL31		bis((diethylphosphino)methyl)ether
P53		1,2-bis(di(2'-ethoxy)ethyl)phosphino)ethane
P65		1,2-bis((methoxymethyl)methylphosphine)ethane

Table 1 (Continued)

5	PL37		1,3-bis(dimethylphosphine)-2,2-bis(methoxymethyl)propane
10	PL40		1,3-bis(dimethylphosphino)-2,2-bis(2',5'-dioxahexyl)propane
15	PL42		1,3-bis(dimethylphosphino)-2,2-bis(ethoxymethyl)propane
20	PL43		1,3-bis(dimethylphosphino)-2,2-bis((2'-methoxy)ethoxymethyl)propane
30	PL46		1,3-bis(dimethylphosphino)-2-(methoxymethyl)-2-((2'-methoxy)ethoxymethyl)propane
35	PL49		4,4-bis((dimethylphosphino)methyl)tetrahydropyran
45	PL50		1,3-bis(dimethylphosphino)-2,2-bis(methoxyethyl)propane
50	P68		1,2-bis(di((2'-methoxy)propyl)phosphino)ethane

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Table 2: Biodistributions of Phenyl diazenide ^{99m}Tc species in Rats

Notebook	IV23	VI12	VI9
Ligand	dmpe	PL28	P46
MEK	60	84	80
RCP (%)	40	70	75
HPLC			
Time P.I.	2 60	2 60	2 60
Heart	0.91 (14) 0.78 (03)	1.12 (11) 0.65 (06)	0.96 (04) 0.80 (02)
Blood	6.98 (71) 1.10 (02)	4.18 (05) 0.46 (04)	7.45 (63) 1.01 (16)
Muscle	22.8 (3.0) 14.0 (3.7)	30.2 (3.0) 27.4 (3.6)	21.4 (3.1) 17.0 (4.0)
Lung	1.88 (14) 0.86 (10)	1.18 (14) 0.62 (05)	1.41 (27) 0.36 (05)
Liver	22.2 (2.6) 10.5 (8)	17.8 (2.9) 5.95 (57)	26.0 (1.0) 6.92 (1.23)
S.I.	13.2 (8) 36.7 (4)	13.2 (1.0) 39.6 (2.7)	11.0 (3.2) 44.0 (1.9)
Kidney	11.2 (8) 9.91 (1.25)	9.41 (0.30) 5.90 (06)	9.62 (48) 2.88 (16)
Bladder & Urine	0.11 (03) 11.3 (4)	0.11 (06) 10.9 (5.9)	0.11 (05) 17.8 (2.6)
Brain	0.06 (01) 0.02 (01)	0.04 (00) 0.02 (00)	0.05 (01) 0.01 (00)
H/B1	1.97 (05) 9.52 (33)	3.97 (32) 21.3 (0.8)	2.05 (29) 13.2 (2.1)
H/Li	0.54 (11) 0.93 (11)	0.82 (19) 1.56 (12)	0.58 (06) 1.79 (30)

Table 2: Biodistributions of Phenyldiazene ^{99m}Tc species in Rats (Continued-2)

Notebook	VI31	LH2.17	LH2.30
Ligand	P46 (HPLC purified)	PL42	PL43
MEK RCP (%)	50	65	26
HPLC	50	70	50
Time P.I.	2 60	2 60	2 60
Heart	1.05 (09) 0.96 (04)	1.22 (30) 1.19 (20)	0.55 (03) 0.26 (03)
Blood	7.00 (0.31) 0.78 (08)	28.6 (1.4) 8.99 (2.28)	21.5 (3.5) 1.14 (16)
Muscle	21.0 (3.1) 21.3 (2.3)	18.1 (0.5) 21.3 (0.3)	21.7 (2.4) 10.9 (1.3)
Lung	1.33 (14) 0.47 (05)	2.56 (33) 1.57 (32)	1.47 (04) 0.22 (03)
Liver	22.1 (2.0) 4.94 (77)	22.8 (3.2) 14.7 (1.6)	21.4 (1.6) 9.08 (2.03)
S.I.	11.5 (3.2) 39.8 (0.3)	7.66 (18) 31.8 (2.0)	8.6 (0.5) 45.6 (6.8)
Kidney	11.1 (2.1) 3.31 (17)	5.35 (46) 3.52 (47)	9.19 (74) 2.32 (32)
Bladder & Urine	1.01 (1.49) 17.0 (4.3)	0.06 (01) 2.61 (23)	0.16 (06) 25.4 (4.6)
Brain	0.04 (00) 0.01 (00)	.	.
H/B1	2.37 (12) 18.9 (1.6)	0.59 (12) 2.13 (43)	0.41 (06) 3.83 (1.03)
H/L1	0.66 (12) 2.77 (36)	0.73 (24) 1.12 (26)	0.38 (03) 0.40 (03)

Table 2: Biodistributions of Phenylidiazide ^{99m}Tc species in Rats (Continued-3)

Notebook	LH2.51	PA11.26	VI28
Ligand	P65	PL50	PL38
MEK			
RCP (%)	60	70	86
HPLC	85	75	80
Time P.I.	2 60	2 60	2 60
Heart	1.20 (11)	0.83 (09)	1.04 (06)
Blood	5.73 (58)	4.38 (25)	4.51 (1.36)
Muscle	27.8 (8.4)	18.7 (2.5)	21.0 (5.1)
Lung	1.61 (18)	1.02 (12)	1.41 (13)
Liver	22.0 (1.8)	34.8 (1.2)	28.4 (1.6)
S.I.	11.2 (2.1)	12.8 (0.7)	11.5 (2.0)
Kidney	12.0 (1.2)	12.0 (0.30)	10.7 (1.9)
Bladder & Urine	0.11 (0.05)	0.09 (03)	0.14 (04)
Brain			0.03 (00)
H/B1	3.33 (30)	2.68 (22)	3.59 (88)
H/L1	0.81 (12)	0.31 (04)	0.48 (01)
			0.00 (00)
			5.81 (1.46)
			62.5 (7.0)
			1.05 (17)

Table 3: Biodistributions of $[Tc^{III}(NNC_6H_4NO_2)(Cl(dmpe)_2)]^+$ in Rats

Notebook		CMAIV78	
Ligand		dmpe	
MEK		86	
RCP (%)		65	
HPLC			
Time P.I.	2		60
Heart	1.15 (22)		0.67 (05)
Blood	5.68 (66)		0.92 (07)
Muscle	26.2 (7.7)		16.8 (1.2)
Lung	2.27 (15)		1.04 (23)
Liver	22.4 (3.9)		12.3 (0.7)
S.I.	13.0 (3.1)		33.8 (3.2)
Kidney	9.47 (25)		9.47 (33)
Bladder & Urine	0.08 (02)		7.28 (1.10)
Brain	0.12 (00)		0.06 (00)
H/B1	3.00 (49)		11.0 (0.9)
H/L1	0.72 (28)		0.76 (12)

Table 4: Biodistributions of ^{99m}Tc -hydrazide (2-) species in Rats and Guinea Pigs

Notebook	PMH2.14	CHAIIV58	CHAIIV61
Ligand	P65	dmpe	dmpe (HPLC purified)
MEK	86	78	83
RCP (%)	90	70	73
HPLC			
Time P.I.	2 60	2 60	2 60
Heart	0.95 (09) 0.69 (03)	1.13 (13) 0.80 (08)	1.25 (08) 0.99 (15)
Blood	4.77 (10) 0.69 (13)	7.84 (47) 1.05 (11)	7.95 (21) 1.05 (21)
Muscle	26.1 (5.8) 20.2 (2.7)	27.9 (4.9) 20.6 (3.2)	26.3 (5.2) 19.3 (4.9)
Lung	1.58 (0.36) 0.33 (02)	2.36 (37) 1.14 (07)	2.40 (0.21) 1.28 (20)
Liver	22.8 (1.4) 9.23 (26)	22.2 (0.6) 11.6 (1.6)	21.1 (1.7) 10.8 (1.9)
S.I.		10.5 (2.2) 30.6 (3.4)	11.9 (3.2) 31.1 (4.5)
Kidney	7.76 (12) 1.95 (15)	9.95 (1.40) 11.1 (0.4)	10.8 (0.6) 11.6 (1.3)
Bladder & Urine		0.08 (01) 6.84 (77)	0.12 (07) 4.70 (93)
Brain		0.05 (01) 0.03 (01)	0.07 (01) 0.04 (01)
H/B1	3.25 (27) 15.0 (3.4)	2.43 (12) 12.2 (1.4)	2.27 (21) 14.2 (2.4)
H/L1	0.64 (06) 1.11 (02)	0.78 (13) 1.06 (13)	0.82 (04) 1.30 (4.1)

Table 4: Biodistributions of ^{99m}Tc -hydrazide (2-) species in Rats and Guinea Pigs (Continued)

Notebook	CHAVI15	CHAVI36	CHAVI36
Ligand	P46	P46* (HPLC purified)	P46 (HPLC purified)
MEK	64	54	RATS
RCP (u)	65	53	54
HPLC			53
Time P.I.	2 60	2 60	60
Heart	0.81 (07)	0.58 (04)	0.97 (06)
Blood	7.10 (0.51)	0.50 (05)	0.27 (02)
Muscle	28.4 (2.5)	18.4 (2.5)	20.0 (1.2)
Lung	1.33 (09)	0.30 (07)	0.36 (10)
Liver	23.3 (0.5)	7.23 (70)	8.29 (67)
S.I.	9.38 (3.20)	44.8 (2.6)	43.6 (2.2)
Kidney	9.37 (52)	2.13 (10)	4.05 (66)
Bladder & Urine	0.18 (10)	19.2 (1.6)	12.7 (1.0)
Brain	0.04 (02)	0.51 (13)	
H/B1	1.65 (08)	16.5 (1.0)	58.7 (7.0)
H/Li	0.48 (03)	1.01 (13)	1.68 (14)
		0.88 (10) * In Guinea Pigs	

55 Examples 17-19

All reactions were performed under an atmosphere of dinitrogen using predried, distilled solvents unless noted otherwise. $[\text{Bu}_4\text{N}][\text{TcOCl}_4]$ was prepared by the literature procedure.²⁸

Example 17

Technetium Diazenido- Starting Materials

5 a) $[\text{TcCl}(\text{NNC}_6\text{H}_4\text{Cl})_2(\text{PPh}_3)_2]$ 9Method 1. From $[\text{Bu}_4\text{N}][\text{TcOCl}_4]$

$[\text{Bu}_4\text{N}][\text{TcOCl}_4]$ (0.134 g, 0.268 mmol), 4- $\text{ClC}_6\text{H}_4\text{NHNH}_2\cdot\text{HCl}$ (0.120 g, 0.67 mmol, 2.5 equivalents),
 10 Et_3N (0.09 ml, 0.67 mmol), and PPh_3 (0.211 g, 0.804 mmol, 3 equivalents) in dry methanol (5 ml) were stirred for 2 hours at room temperature. The khaki solid was collected by filtration, washed with methanol and ether and dried. (yield 0.134 g, 53%). The product could be recrystallised from $\text{CH}_2\text{Cl}_2/\text{MeOH}$ yielding bright orange crystals. (Found: C,61.23; H,3.98; N,6.05; Cl,11.74. $\text{TcC}_{48}\text{H}_{38}\text{N}_4\text{P}_2\text{Cl}_3$ requires C,61.45; H,4.08; N,5.97; Cl,11.34 %). HPLC retention time 9.4 minutes, single species. ν_{max} . (KBr plates, nujol mull)
 15 $1600, 1555\text{ cm}^{-1}$ (NN). ^{31}P NMR (CDCl_3) 30.27 ppm singlet.

Method 2. From $[\text{NH}_4][\text{TcO}_4]$

Aqueous $[\text{NH}_4][\text{TcO}_4]$ (0.5 ml, 0.181 mmol) was evaporated to dryness in *vacuo*. $\text{ClC}_6\text{H}_4\text{NHNH}_2\cdot\text{HCl}$
 20 (0.142g, 0.793 mmol) in dry methanol (2.5 ml) was added with stirring to give an orange solution after 10 minutes. Solid PPh_3 (0.204 g, 0.778 mmol) was added and the mixture heated under reflux for 1.5 hours. After cooling to room temperature the khaki solid was collected by filtration and washed with ether (yield 0.113g, 67%). The product could be crystallised from $\text{CH}_2\text{Cl}_2/\text{MeOH}$ to yield an orange crystalline solid which has an identical IR spectrum to an authentic sample of 9 prepared from $[\text{TcOCl}_4]^-$.

25 b) $[\text{Tc}(\text{NNC}_6\text{H}_4\text{CH}_3)_2(\text{PPh}_3)_2]$ 10

$[\text{Bu}_4\text{N}][\text{TcOCl}_4]$ (0.178 g, 0.356 mmol), $\text{CH}_3\text{C}_6\text{H}_4\text{NHNH}_2\cdot\text{HCl}$ (0.282 g, 1.78 mmol, 5 equivalents), Et_3N
 30 (0.25 ml, 1.78 mmol), and PPh_3 (0.280 g, 1.07 mmol, 3 equivalents) were stirred in dry methanol (5 ml) overnight to give a khaki suspension. The product was collected by filtration, washed with ether and dried (yield 0.122 g, 40%). HPLC retention time 10.4 minutes, one major species. Analysis on the crude material gave (Found: C,64.1; H,4.6; N,5.9; Cl,3.53. $\text{TcC}_{50}\text{H}_{44}\text{N}_4\text{P}_2\text{Cl}$ requires C,66.93; H,4.94; N,6.24; Cl,3.95%). ^1H NMR (CDCl_3) 2.29[6H, s, 2 x CH_3], 6.5-8.0 [38H, m, phenyl H]. ^{31}P NMR (CDCl_3) 28.6 ppm singlet. ν_{max} .
 1620, 1570, 1535 cm^{-1} (NN). The product may be recrystallised from $\text{CH}_2\text{Cl}_2/\text{MeOH}$.

35 c) $[\text{TcCl}_2(\text{NNC}_6\text{H}_4\text{NO}_2)(\text{PPh}_3)_2]$ 11

$[\text{Bu}_4\text{N}][\text{TcOCl}_4]$ (0.152 g, 0.304 mmol), $\text{O}_2\text{NC}_6\text{H}_4\text{NHNH}_2$ (0.116 g, 0.76 mmol, 2.5 equivalents), and
 40 PPh_3 (0.239 g, 0.912 mmol, 3 equivalents) in dry methanol (5 ml) were stirred overnight to give a pale orange solid which was collected by filtration (yield 0.223 g, 77%). This was recrystallised from $\text{CH}_2\text{Cl}_2/\text{MeOH}$ to give a lime-green solid (0.151 g, 52%). ν_{max} . 1620, 1600 (NN), 1555 (NO_2), 1335 (NO_2) cm^{-1} . ^1H NMR (CDCl_3) 3.4 [MeOH], 7.0-8.0[phenyl H]. ^{31}P NMR (CDCl_3) 30.0 ppm singlet. HPLC retention time 10.4 minutes. (Found: C,57.65; H,4.18; N,4.94; Cl,8.60. Found: C,57.42; H,4.24; N,4.95; Cl,7.95. $\text{TcC}_{43}\text{H}_{38}\text{N}_3\text{Cl}_2\text{O}_3\text{P}_2$ requires C,58.92; H, 4.37; N,4.79; Cl,8.09%).

45 Example 18

Substitution Chemistry of the Technetium Diazenido-Starting Materials

50 a) $[\text{TcCl}(\text{NNC}_6\text{H}_4\text{Cl})(\text{dppe})_2][\text{BPh}_4]$ 12

9 (0.098 g, 0.104 mmol) and dppe (0.104 g, 0.26 mmol, 2.5 equivalents) in methanol-toluene (1:1, 4 ml)
 were heated under reflux for 3 hours to give a dark orange solution. Solid NaBPh_4 (0.035 g, 1 equivalent)
 was added with stirring to precipitate an orange solid. The product was collected by filtration (yield 0.117 g,
 55 77%). The crude product could be recrystallised from $\text{CH}_2\text{Cl}_2/\text{ether}$. (Found: C,70.55; H,5.34; N,2.17;
 Cl,4.72. $\text{TcC}_{80}\text{H}_{72}\text{N}_2\text{BP}_4\text{Cl}_2$ requires C,70.34; H,5.31; N,2.05; Cl,5.19%). HPLC retention time 14 minutes.
 ν_{max} . 1575, 1665 cm^{-1} (NN). ^1H NMR (CDCl_3) 2.68[8H, broad m, 2 x $-\text{CH}_2\text{CH}_2-$], 6.5-7.5[64H, broad
 unresolved m, phenyl H].

b) $[\text{TcCl}(\text{NNC}_6\text{H}_4\text{Cl})(\text{dppe})_2][\text{PF}_6]$ 12a

This was prepared in an analogous fashion to 12 using 9 (0.101 g, 0.107 mmol) and dppe (0.107 g, 0.269 mmol) in methanol/toluene (1:1, 4 ml) under reflux for 1 hour. $[\text{NH}_4][\text{PF}_6]$ (0.018 g, 0.110 mmol) was added with stirring to the filtered reaction mixture to give 12a (yield 0.059 g, 43%). This could be recrystallised from $\text{CH}_2\text{Cl}_2/\text{MeOH}$ (Found: C,55.44; H,4.27; N,2.48; Cl, 6.35. $\text{TcC}_{58}\text{H}_{44}\text{N}_2\text{P}_5\text{Cl}_2\text{F}_6$ requires C,57.68; H,3.67; N,2.32; Cl,5.87%).

c) $[\text{TcCl}(\text{NNC}_6\text{H}_4\text{NO}_2)(\text{dppe})_2][\text{BPh}_4]$ 13

11 (0.051 g, 0.06 mmol) and dppe (0.060 g, 0.151 mmol, 2.5 equivalents) in methanol/toluene (1:1, 3ml) were heated under reflux for 1 hour to give an orange-red solution. After cooling to room temperature solid NaBPh_4 (0.02 g, 1 equivalent) was added with stirring to precipitate the product as an orange solid. This was collected by filtration and washed with MeOH and Et_2O (yield 0.06 g, 72%). The product was recrystallised from $\text{CH}_2\text{Cl}_2/\text{Et}_2\text{O}$ (yield 0.042 g, 50%) as an orange crystalline solid. ν_{max} 1645s, 1600w (NN), 1570 (NO_2), 1340 (NO_2) cm^{-1} . HPLC retention time 14.2 minutes, single peak. (Found: C,67.65; H,5.12; N,2.93; Cl,4.14. $\text{TcC}_{82}\text{H}_{72}\text{N}_3\text{O}_2\text{Cl-P}_4\text{B}_1/2\text{CH}_2\text{Cl}_2$ requires C,68.66; H,5.10; N,2.91; Cl,4.91%).

d) $[\text{Tc}(\text{NNC}_6\text{H}_4\text{Cl})(\text{S}_2\text{CNMe}_2)_2(\text{PPh}_3)]$ 14

9 (0.139 g, 0.148 mmol) and $\text{NaS}_2\text{CNMe}_2$ (0.08 g, 0.444 mmol, 3 equivalents) in absolute ethanol (2 ml) were heated under reflux for 1.5 hours. The orange solid was collected by filtration after cooling (yield 0.072g) and redissolved in CH_2Cl_2 before passage down a Fluorsil column eluting the orange band with CH_2Cl_2 . This eluate was evaporated to dryness and the residue recrystallised from $\text{CH}_2\text{Cl}_2/\text{Et}_2\text{O}$ to give dark orange crystals (yield 0.072 g, 66%). HPLC retention time 13.6 minutes, single species. (Found: C,45.82; H,4.09; N,6.79; Cl,6.25. Found: C,45.99; H,4.04; N,6.77. $\text{TcC}_{30}\text{H}_{31}\text{N}_4\text{ClS}_4\text{P}_1/2\text{CH}_2\text{Cl}_2$ requires C,46.74; H,4.11; N,7.15; Cl,9.05. $\text{TcC}_{30}\text{H}_{31}\text{N}_4\text{ClS}_4\text{P}_1/4\text{CH}_2\text{Cl}_2$ requires C,47.65; H,4.16; N,7.35; Cl,6.97%). ^1H NMR (CDCl_3) 2.92[3H, s, CH_3], 3.06[3H, s, CH_3], 3.31 [3H, s, CH_3], 3.39[3H, s, CH_3], 5.27[CH_2Cl_2], 6.8-7.7[19H, m, phenyl H]. ^{31}P NMR (CDCl_3) no signal was observed in this sample at room temperature.

e) $[\text{TcCl}(\text{NNC}_6\text{H}_4\text{Cl})(\text{maltol})(\text{PPh}_3)_2]$ 15

9 (0.145 g, 0.155 mmol) and maltol (0.059 g, 0.465 mmol, 3 equivalents) in absolute ethanol (2 ml) were heated under reflux for 2 hours. After cooling to room temperature the orange product was collected by filtration and washed with ethanol. The product was recrystallised from $\text{CH}_2\text{Cl}_2/\text{ether}$ (yield 0.03 g, 21%) as dark orange crystals. (Found: C,59.68; H,4.11; N,3.03; Cl,7.73. $\text{TcC}_{48}\text{H}_{39}\text{N}_2\text{Cl}_2\text{O}_3\text{P}_2$ requires C,62.41; H,4.23; N,3.03, Cl,7.68%). ν_{max} 1615s, 1560 cm^{-1} . ^1H NMR (CDCl_3) 2.21[3H, s, CH_3], 5.63[1H, d, $J_{\text{HH}} = 4$ Hz, C=CH], 6.92[1H, d, $J_{\text{HH}} = 4$ Hz, C=CH], 7.0-8.0[34H, m phenyl H]. ^{31}P NMR (CDCl_3) 30.0 ppm singlet. HPLC retention time 10 minutes.

f) $[\text{Tc}(\text{NNC}_6\text{H}_4\text{Cl})(\text{salen})(\text{PPh}_3)]$ 16

9 (0.100 g, 0.107 mmol), salen H_2 (0.032 g, 0.119 mmol, 1.1 equivalents), and Et_3N (0.40 ml, 0.259 mmol, 2.2 equivalents) in dry methanol/toluene (1:1, 3 ml) were heated under reflux for 2 hours. After cooling, addition of ether gave a khaki-green solid which was collected by filtration, washed with ether and dried (yield 0.052 g, 63%). The product could be recrystallised from $\text{CH}_2\text{Cl}_2/\text{heptane}$ as very dark green crystals. (Found: C,61.77; H,4.41; N,7.17; Cl,4.77. $\text{TcC}_{40}\text{H}_{33}\text{N}_4\text{PO}_2\text{Cl}$ requires C,62.63; H,4.34; N,7.30; Cl,4.62%). ν_{max} 1600, 1610, 1620 (NN), 1540 (C=N) cm^{-1} . ^1H NMR (CDCl_3) 4.0[4H, broad m, $-\text{CH}_2\text{CH}_2-$], 6.0-7.6[27H, broad m, phenyl H], 8.14[2H, s, N=CH]. ^{31}P NMR (CDCl_3) no signal was observed at room temperature. HPLC retention time 11.6 minutes.

g) $[\text{Tc}(\text{NNC}_6\text{H}_4\text{Cl})_2(\text{N}_2\text{S}_2)]_x$ 17

$\text{N}_2\text{S}_2 = (\text{HSCH}(\text{Me})\text{CONHCH}_2-)_2$

9 (0.083 g, 0.088 mmol), N_2S_2 (0.023 g, 0.097 mmol, 1.1 equivalents), and Et_3N (0.05 ml, 0.34 mmol, 4 equivalents) in dry methanol (2 ml) were heated under reflux for 1 hour to give a dark brown-green solution. The solvent was removed *in vacuo* and the brown oil triturated with isopropanol to give a dark brown solid product (yield 0.011 g). The product was too insoluble for satisfactory recrystallisation and analysis by

NMR, but appeared to be diamagnetic. HPLC retention time 12.2 minutes. (Found: C,40.36; H,4.40; N,9.19; Cl,11.97. $\text{TcC}_{20}\text{H}_{24}\text{N}_4\text{Cl}_2\text{S}_2\text{O}_2$ requires C,40.96; H,4.12; N,9.55; Cl,12.09%).

Example 19

5

Technetium Imido Complexes



10 Method 1. From $[\text{NH}_4][\text{TcO}_4]$

Aqueous $[\text{NH}_4][\text{TcO}_4]$ (1 ml, 0.343 mmol), 2- $\text{HO}_2\text{CC}_6\text{H}_4\text{NH}_3\text{Cl}$ (2-carboxyaniline hydrochloride) (0.298 g, 1.715 mmol, 5 equivalents), and PPh_3 (0.360g, 1.372 mmol, 4 equivalents) in reagent grade methanol (10 ml) were stirred overnight to give a bright green precipitate. The product was collected by filtration, washed
15 with MeOH, ether and dried *in vacuo* (yield 0.139 g, 50%). (Found: C,63.30; H,4.44; N,1.77. $\text{TcC}_4\text{H}_3\text{NO}_2\text{P}_2\text{Cl}_2$ requires C,62.33; H,4.14; N,1.67%). The product was soluble in DMF and CH_2Cl_2 .

Method 2. From $[\text{Bu}_4\text{N}][\text{TcOCl}_4]$

20 $[\text{Bu}_4\text{N}][\text{TcOCl}_4]$ (0.262 g, 0.525 mmol), anthranilic acid (0.72 g, 5.25 mmol, 10 equivalents), and PPh_3 - (0.48 g, 1.84 mmol, 3.5 equivalents) in absolute ethanol (20 ml) were heated under reflux for 2 hours. The hot solution was filtered (air) and taken to dryness *in vacuo*. The residue was then triturated with ether and the solid green product isolated after filtration was recrystallised from EtOH/hexane (yield 0.114 g, 26%). ^{31}P NMR (DMSO) 31.2 ppm singlet.

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Claims

1. A complex of technetium (^{99}Tc or $^{99\text{m}}\text{Tc}$) which contains the moiety $\text{Tc}=\text{NR}$, $\text{Tc}-\text{N}=\text{NY}$ or $\text{Tc}(-\text{N}=\text{NY})_2$, and a ligand which confers biological target-seeking properties on the complex,
 wherein
 R represents an aryl group, a substituted or unsubstituted alkyl group, or the grouping $=\text{NR}^1\text{R}^2$;
 Y represents an aryl group or a substituted or unsubstituted alkyl group;
 and
 R^1 and R^2 are hydrogen, aryl groups or substituted or unsubstituted aliphatic or cyclic alkyl groups,
 and may be both the same or different, provided that both are not hydrogen.
2. A complex as claimed in claim 1 of the formula $\text{L}_n\text{Tc}=\text{NR}$,
 wherein
 L represents a mono-dentate or multi-dentate ligand;
 n is 1, 2, 3 or 4;
 and
 R is as previously defined.
3. A complex as claimed in claim 1 of the formula $\text{L}_n\text{Tc}-\text{N}=\text{NY}$,
 wherein
 L represents a mono-dentate or multi-dentate ligand;
 n is 1, 2, 3 or 4;
 and
 Y is as previously defined.
4. A complex as claimed in claim 1 of the formula $\text{L}_n\text{Tc}(-\text{N}=\text{NY})_2$,
 wherein
 L represents a mono-dentate or multi-dentate ligand;
 n is 1, 2, 3 or 4;
 and
 Y is as previously defined.
5. A complex as claimed in any one of claims 1 to 4, wherein the alkyl group is substituted with oxygen, nitrogen, sulphur and/or phosphorus.
6. A complex as claimed in any one of the preceding claims, wherein the ligand is selected from phosphines and arsines of the general formula

$$\text{Q}_2\text{B}(\text{CD}_2)_n\text{BQ}_2$$
 wherein
 Q represents hydrogen, an aryl group or a substituted or unsubstituted alkyl group;
 B is P or As;
 (CD_2) is a substituted or unsubstituted methylene group;
 and
 n is 1, 2, 3 or 4.

7. A complex as claimed in any of the preceding claims, useful as a radiopharmaceutical, wherein the biological target-seeking properties of the complex are determined by the nature of the ligands present and/or of the substituents R and Y.
- 5 8. A method of preparing a complex of technetium (^{99}Tc or $^{99\text{m}}\text{Tc}$) which contains the moiety $\text{Tc}=\text{NR}$, $\text{Tc}-\text{N}=\text{NY}$ or $\text{Tc}(\text{N}=\text{NY})_2$, wherein R and Y are as defined in claim 1, which method comprises the derivatisation of a technetium oxo-containing species by condensation with a hydrazine, an amine, an isocyanate, a sulphinylamine or a phosphinimine.
- 10 9. A method of preparing a complex of technetium (^{99}Tc or $^{99\text{m}}\text{Tc}$) which contains the moiety $\text{Tc}=\text{NR}$, $\text{Tc}-\text{N}=\text{NY}$ or $\text{Tc}(\text{N}=\text{NY})_2$, wherein R and Y are as defined in claim 1, which method comprises the reaction of a hydrazine or amine with a complex containing technetium-halogen bonds.
10. A radiopharmaceutical which includes a complex of technetium as claimed in any one of claims 1 to 7.

Patentansprüche

1. Ein Technetiumkomplex (^{99}Tc oder $^{99\text{m}}\text{Tc}$), der den Strukturteil $\text{Tc} = \text{NR}$, $\text{Tc}-\text{N} = \text{NY}$ oder $\text{Tc}(\text{N} = \text{NY})_2$ enthält, und einen Liganden, der dem Komplex biologische, einer Zielfindung entsprechende Eigenschaften verleiht,
 20 wobei
 R eine Arylgruppe, eine substituierte oder unsubstituierte Alkylgruppe, oder die Gruppierung $= \text{NR}^1\text{R}^2$ repräsentiert;
 Y eine Arylgruppe oder eine substituierte oder unsubstituierte Alkylgruppe repräsentiert;
 25 und
 R^1 und R^2 für Wasserstoff, Arylgruppen oder substituierte oder unsubstituierte aliphatische oder zyklische Alkylgruppen stehen, und gleich oder unterschiedlich sein können, vorausgesetzt beide sind nicht Wasserstoff.
- 30 2. Ein Komplex wie in Anspruch 1 dargestellt mit der Formel $\text{L}_n\text{Tc} = \text{NR}$,
 wobei
 L einen einzähnigen oder mehrzähnigen Liganden repräsentiert;
 n für 1, 2, 3 oder 4 steht;
 und
 35 R wie oben definiert ist.
3. Ein Komplex wie in Anspruch 1 dargestellt mit der Formel $\text{L}_n\text{Tc}-\text{N} = \text{NY}$,
 wobei
 L einen einzähnigen oder mehrzähnigen Liganden repräsentiert;
 40 n für 1, 2, 3 oder 4 steht;
 und
 Y wie oben definiert ist.
4. Ein Komplex wie in Anspruch 1 dargestellt mit der Formel $\text{L}_n\text{Tc}(\text{N} = \text{NY})_2$,
 45 wobei
 L einen einzähnigen oder mehrzähnigen Liganden repräsentiert;
 n für 1, 2, 3 oder 4 steht;
 und
 Y wie oben definiert ist.
- 50 5. Ein Komplex wie in den Ansprüchen 1 bis 4 dargestellt, wo die Alkylgruppe durch Sauerstoff, Stickstoff, Schwefel und/oder Phosphor substituiert wird.
6. Ein Komplex wie in den vorausgegangenen Ansprüchen dargestellt, wo der Ligand aus Phosphinen und
 55 Arsinen der allgemeinen Formel
 $\text{Q}_2\text{B}(\text{CD}_2)_n\text{BQ}_2$ gewählt wird,
 wobei
 Q Wasserstoff, eine Arylgruppe oder eine substituierte oder unsubstituierte Alkylgruppe darstellt;

B für P oder As steht;
 (CD₂) eine substituierte oder unsubstituierte Methylengruppe ist;
 und
 n für 1, 2, 3 oder 4 steht.

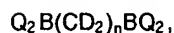
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7. Ein Komplex wie in den vorangegangenen Ansprüchen dargestellt, der als Radiopharmaceutikum von Nutzen ist, wo die biologischen einer Zielfindung entsprechenden Eigenschaften des Komplexes durch die Natur der anwesenden Liganden und/oder der Substituenten R und Y bestimmt werden.
- 10 8. Eine Methode zur Darstellung eines Technetium-Komplexes (⁹⁹Tc oder ^{99m}Tc), der den Strukturteil Tc = NR, Tc-N = NY oder Tc(-N=NY)₂ enthält, wo R und Y wie in Anspruch 1 definiert sind, wobei die Methode die Derivatisierung einer Technetium-oxo enthalten Spezies durch Kondensation mit einem Hydrazin, einem Amin, einem Isocyanat, einem Sulphinylamin oder einem Phosphinimin umfaßt.
- 15 9. Eine Methode zur Darstellung eines Technetium-Komplexes (⁹⁹Tc oder ^{99m}Tc), der den Strukturteil Tc = NR, Tc-N=NY oder Tc(-N=NY)₂ enthält, wo R und Y wie in Anspruch 1 definiert sind, wobei die Methode die Reaktion eines Hydrazins oder Amins mit einem Komplex, der Technetium-Halogen-Bindungen enthält, umfaßt.
- 20 10. Ein Radiopharmaceutikum, das einen wie in den Ansprüchen 1 bis 7 beanspruchten Technetium-Komplex beinhaltet.

Revendications

- 25 1. Un complexe de technétium (⁹⁹Tc ou ^{99m}Tc) contenant la partie Tc = Nr, Tc-N = NY ou Tc(-N = NY)₂ et un ligand conférant des propriétés de recherche de cibles biologiques au complexe.
 où
 R représente un groupe aryle, un groupe alkyle substitué ou non substitué ou le groupement = Nr'R²;
 30 Y représente un groupe aryle ou un groupe alkyle substitué ou non substitué;
 et où
 R¹ et R² sont des groupes hydrogène, aryle ou des groupes alkyles aliphatiques ou cycliques substitués ou non substitués pouvant être identiques ou différents à condition qu'ils ne soient pas simultanément hydrogène.
- 35 2. Un complexe selon la revendication 1 suivant la formule L_nTc = NR,
 où
 L représente un ligand monodenté ou multidenté;
 n est 1, 2, 3 ou 4;
 40 et où
 R est conforme à la définition précédente.
3. Un complexe selon la revendication 1, suivant la formule L_nTc-N = NY,
 où
 45 L représente un ligand monodenté ou multidenté;
 n est 1, 2, 3 ou 4;
 et où
 Y est conforme à la définition précédente.
- 50 4. Un complexe selon la revendication 1 suivant la formule L_nTc(-N = NY)₂,
 où
 L représente un ligand monodenté ou multidenté;
 n est 1, 2, 3 ou 4;
 et où
 55 Y est conforme à la définition précédente.
5. Un complexe selon l'une des revendications 1 à 4, où le groupe alkyle est substitué par de l'oxygène, de l'azote, du soufre et/ou du phosphore.

6. Un complexe selon l'une des revendications précédentes où le ligand est sélectionné parmi des phosphines et des arsines appartenant à la formule



où

Q représente l'hydrogène, un groupe aryle ou un groupe alkyle substitué ou non substitué;

B est P ou As;

(CD₂) est un groupe méthylène substitué ou non substitué

et où

n est 1, 2, 3 ou 4.

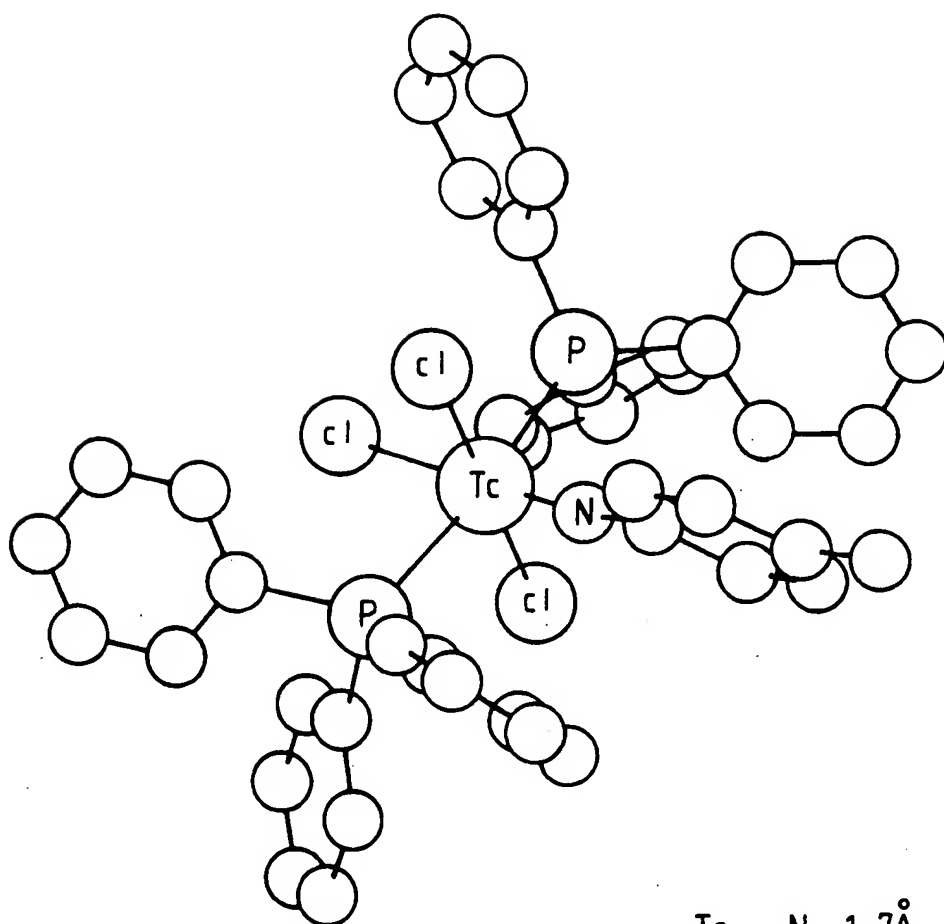
7. Un complexe selon l'une des revendications précédentes utiles à titre de produits radiopharmaceutiques et dont les propriétés de recherche de cibles biologiques sont déterminées par la nature des ligands présents et/ou des substituants R et Y.

8. Une méthode de préparation d'un complexe de technétium (^{99m}Tc ou ^{99m}Tc) contenant la partie Tc=NR, Tc-N=NY ou Tc(-N=NY)₂, où R et Y sont conformes à la revendication 1, cette méthode comprenant la transformation d'une espèce de technétium contenant un oxo par condensation avec une hydrazine, une amine, un isocyanate, une sulphinylamine ou une phosphinimine.

9. Une méthode de préparation d'un complexe de technétium (^{99m}Tc ou ^{99m}Tc) contenant la partie Tc=NR, Tc-N=NY ou Tc(-N=NY)₂, où R et Y sont conformes à la définition de la revendication 1, cette méthode comprenant la réaction d'une hydrazine ou d'une amine avec un complexe contenant des liaisons technétium-halogène.

10. Un produit radiopharmaceutique comprenant un complexe de technétium tel que revendiqué par l'une des revendications de 1 à 7.

Fig 1 Pluto Plot of $[\text{Tc}(\text{Ntol})\text{Cl}_3(\text{PPh}_3)_2]$



Tc - N, 1.7Å
Tc - N-C, 168Å